The Management of Cytokine Storm in COVID-19

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ABSTRAK

Badai sitokin pada infeksi COVID-19 adalah keadaan dimana terjadi respons imun yang berlebihan terhadap adanya stimulus dari luar dengan patogenesis yang kompleks. Badai sitokin menyebabkan terjadinya perburukan penyakit yang terjadi secara cepat dengan angka mortalitas yang tinggi. Bukti yang ada menunjukkan bahwa progresivitas penyakit berkaitan erat dengan adanya peningkatan sitokin pada pasien pneumonia akibat SARS-CoV2. Terapi yang efektif dan aman dibutuhkan untuk mengatasi hiperinflamasi sehingga diharapkan dapat mencegah terjadinya kematian. Hingga saat ini belum ada terapi yang spesifik untuk mengatasi infeksi COVID-19. Studi pendahuluan telah memperlihatkan bahwa terapi dengan imunomodulator dan terapi imunosupresif dapat dipertimbangkan sebagai terapi pilihan pada infeksi COVI-19 yang berat. Dalam artikel ini diulas mengenai patogenesis terjadinya badai sitokin pada infeksi COVID-19 beserta terapinya, sehingga diharapkan dapat digunakan sebagai pedoman dalam tatalaksana pasien.

Kata kunci: badai sitokin, hiperinflamasi, COVID-19.

ABSTRACT

Cytokine storm in COVID-19 infection is an excessive immune response to external stimuli where the pathogenesis is complex. The disease progresses rapidly and the mortality is high. Certain evidence shows that the severe deterioration of some patients has been closely related to the strong upregulation of cytokine production in SARS-Co-V2 induced pneumonia with an associated cytokine storm syndrome. Identification of existing approved therapy with proven safety profile to treat hyperinflammation is critical unmet need in order to reduce COVID-19 associated mortality. To date, no specific therapeutic drugs are available to treat COVID-19 infection. Preliminary studies have shown that immune-modulatory or immune suppressive treatments might be considered as treatment choices for COVID-19, particularly in severe disease. This article review the pathogenesis and treatment strategies of COVID-19 virus-induced inflammatory storm in attempt to provide valuable medication guidance for clinical treatment.

Keywords: cytokine storm, hyperinflammation, COVID-19.

INTRODUCTION

Cytokine storm (CS) refers to excessive and uncontrolled release of proinflammatory cytokine. Clinically it commonly presents as systemic inflammation, multiple organ failure and high inflammatory parameters. While most patients with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires hospitalization and oxygen support

and 5% have critical disease with complication such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, acute kidney injury, cardiac injury and multiple organ failure. Older age, smoking and underlying noncommunicable diseases such as hypertension, cardiac disease, chronic lung disease and cancer have been reported as risk factors for severe disease and death. Multivariate analyses have confirmed that older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1μg/L on admission were associated with higher mortality. The effective antiviral responses of the host innate and adaptive immunity, including the production of various proinflammatory cytokines, the activation of T cells, CD4 and CD8+ T cells are essential for controlling the viral replication, limiting the spread of virus, inflammation and cleaning the infected cells.[1,2]

PATHOGENESIS

Virus SARS-CoV-2 transmitted via droplet, direct contact and fomites. Mediated by transmembrane protease serine-type 2 (TMPRSS2), SARS-CoV-2 S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter and infect cells. Viral entry followed by replication RNA genomes translation. Ribonucleic acid synthesis occurs on the cellular membrane to mediate the viral replication and form a new virus. Angiotensin-converting enzyme 2 presents on the oral and nasal mucosal, nasopharyngeal, lung, stomach, small intestine and large intestine. skin, thymus, bone marrow, spleen, liver, kidney, brain, blood vessels endothelial cells and smooth muscle cells.[3] Multiplication progressed in the lower respiratory tract and the gastrointestinal mucosa causing slight viremia. With adequate immunity to handle the infection process, the patient may appear asymptomatic.[4] The effective antiviral respons of the host innate and adaptive immunity are essential for controlling the viral replication, limiting the spread of virus, inflammation and cleaning the infected cells. A rapid and well-coordinated innate response is the first line of defense against viral infection. However, dysregulated and excessive immune respons

may cause immune damage to the human body. Furthermore, the tissue injury caused by the virus could induced the exaggerated production of proinflamatory cytokines, recruitment of proinflamatory macrophages and granulocytes. This may results in cytokines storm termed as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis leading to further tissue damage.[5] A cytokine storm is the primary mechanism of ARDS due to uncontrolled systemic inflammation induces by proinflammatory cytokines (IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α,) and chemokines. The plasma level of IL-6 considered as a significant cytokine contributing to MAS, increased in patients with severe COVID-19 infection.[5] Increasing of inflammatory cytokine release due to uncontrolled activation of immune reponses is likely not limited to the innate mechanisms. As a result of proinflamatory cytokine expression and the presence of nuclear antigen from cell and tissue damage, adaptive immune cells may become activated and trigger a second wave of inflammation potentially in patients who deteriorate after 7 - 10 days of infection. Indeed, adaptive immune cells, namely T lymphocytes which are observed in lung tissue sections of COVID-19 patients with ARDS, may drive inflammation at later disease stages.[6]

CLINICAL MANIFESTATIONS

Infection of COVID-19 exhibits 3 grades of increasing severity, which correspond with distinct clinical findings, response to therapy and clinical outcome (**Figure 1**).[7,8]

Stage I (Mild) – Early Infection

The initial stage occurs at the time of inoculation and early establishment of disease. For most patients, this involves an incubation period associated with mild and often non-specific symptoms, such as malaise, fever and a dry cough. During this period, SARS-CoV-2 multiplies and establishes residence in the host, primarily focusing on the respiratory system. Initially SARS-CoV-2 binds to its target using the angiotensin-converting enzyme 2 receptor on human cells. These receptors are abundantly present on human lung and small intestine

epithelium and the vascular endothelium. As a result of the airborne method of transmission and affinity for pulmonary angiotensin-converting enzyme 2 receptors, the infection usually presents with mild respiratory and systemic symptoms.

Stage II (Moderate) – Pulmonary Involvement (IIa) Without and (IIb) With Hypoxia

In the second stage of establishes pulmonary disease, viral multiplication and localized inflammation occur in the lung tissue. During this stage, patients develop a viral pneumonia with cough, fever and possibly hypoxia (defined as PaO2/FiO2 <300 mmHg). Imaging with chest roentgenogram or computed tomography reveals bilateral infiltrates or ground-glass opacities. Blood tests reveal increasing lymphopenia, along with elevation of makers for systemic inflammation. It is at this stage that most patients with COVID-19 would need to be hospitalized for close observation and management.

Stage III (Severe) – Systemic Hyperinflammation

A minority of COVID-19 patients will transition into the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation seem to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts. Studies have revelaled that

inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, TNF- α, granulocyte colony-stimulating factor, macrophage inflammatory protein 1, C-reactive protein, ferritin and D-dimer are significantly elevated in those patients with more severe disease. A form akin to secondary hemophagocytic lymphohistiocytosis may occur in patients in this advanced stage of the disease. In this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable. Systemic organ involvement, even myocarditis would manifest during this stage.

DIAGNOSIS

Patients with confirmed COVID-19 infection may have severe cytokine release syndrome with the following criteria: persistent fever for more than 3 days, two biomarkers elevation (cytokines, CRP, ferritin) and at least one organ toxicity (hypotension that requiring vasoactive drugs, hypoxia [SpO2 < 90% in room air]) and neurologic disorder including mental status changes, obtundation and seizure. Cytokines and CRP examination can serve as a diagnostic tool to determine the disease severity. Ideally, cytokines profile examination should be performed in order to determine the most suitable immunomodulator treatment . In the acute phase, the liver responds to IL-6 activity by synthesizing CRP.[9,10] C-reactive protein examination is useful
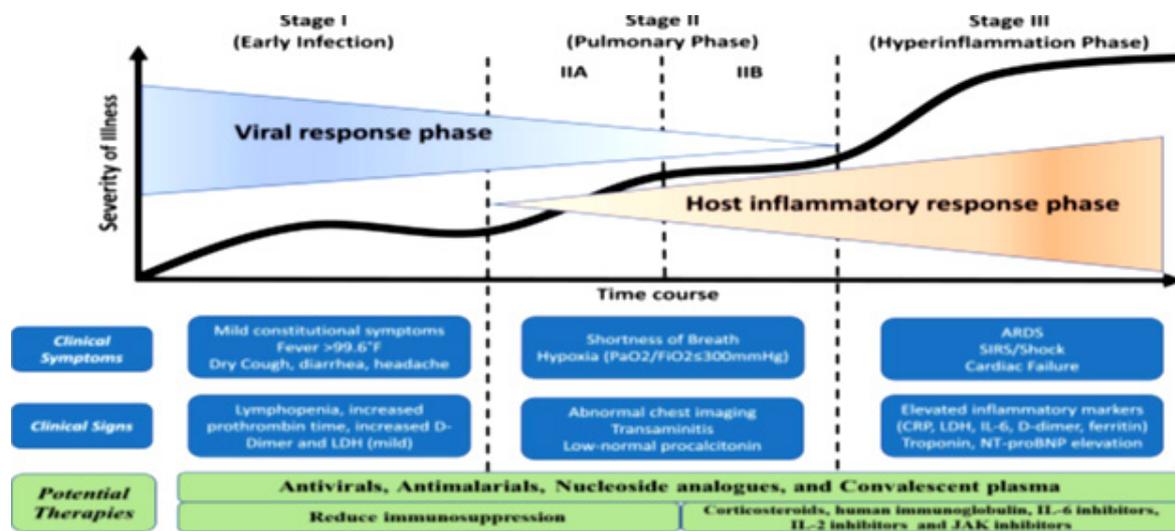

Figure 1. Classification of COVID-19 disease states and potential therapeutic targets.

to monitor the progress of the disease, faster to examine, economical and widely available compared to cytokine levels measurement. Clinical symptoms approach and biomarker examination are usefull to predict the severity of disease. Chest X-ray examination may reveal diffuse infiltrate on both lung and from lung CT scan may also show diffuse ground-glass opacity on both lung with or without crazy-paving pattern consistent with ARDS.[9,10]

TREATMENT

Drugs for COVID-19 infection treatment mostly come from observational study with few clinical trials without provide high-quality evidence. Based on WHO guideline for clinical management of COVID-19, treatment with antiviral and immunomodulator should be in context of clinical trial. Therefore for the legal aspect, outside of clinical trial the the investigational therapeutics should be given with the following criteria: treatment has been suggested by qualified scientific advisory committee on the basis of a favourable risk-benefit analysis, as well as an appropriately qualified ethics committee have approved such use, the patiets informed consent is obtained and the emergency use of the drugs is monitored and the results are documented and shared in timely manner with the wider medical and scientific community.[1] Principally, cytokine storm treatment mainly focused on immunosuppression alongside control measures on triggering factors. Drugs given to COVID-19 infection consisting of antiviral therapy, corticosteroid, antibiotic, venous thromboembolism prophylaxis and therapy with immunomodulators (chloroquine/hydroxychloroquine, azithromycin, tocilizumab, intravenous immunoglobulin (IVIG), plasma convalescen therapy and stem cells therapies). Beside such medical treatment, supportive treatment with oxygen therapy, noninvasive ventilation and ventilatory support should be performed simultaneously according to the severity of the disease.[1,11]

Antiviral Therapy

At present, there is no definitive antiviral treatment for COVID-19. Available drug options that come from the clinical experience of treating SARS, MERS and other previous Influenza virus have been used for treatment of COVID-19 patients. Lopinavir as a proteinase inhibitors, restains the action of 3-chymotrypsin-like protease (3CLpro) that plays an important role in processing the viral RNA, and disrupts viral replication process and their release from host cells. Its usually combined with ritonavir that can enhance the antiviral activity of lopinavir. The recommended regimen is lopinavir 200 mg/ritonavir 50 mg, 2 tablets twice daily for 14 days or for 7 days after become asymptomatic. Favipiravir an oral antiviral drug, is a synthetic prodrug of a purine nucleotide. It undergoes intracellular ribosylation and phosphorylation into the active form of favipirapir ribofuranosyl-5'-triphosphate (favipirapir-RTP). Favipirapir-RTP can inhibits RNA-dependent RNA polymerase (RdRp) activity, resulting in inhibition of transcription and replication of the viral genome. Favipiravir is given orally for 7 – 10 days, a maximum of 14 days with a loading dose 1600 mg every 12 hours for the first day, followed by a maintenance dose 600 mg every 12 hours (days 2 to 7 or 10). Remdesivir is prodrug of adenosine analogue that undergoes metabolism to an active C-adenosine nucleoside triphosphate anolaque. The active form (Favipirapir-RTP) competes with adenosine triphosphate and incorporates with the RNA strand, causing premature termination or RNA synthesis and halting the RNA replication. The initial dose is a single 200 mg loading dose, followed by 100-mg daily infusion for 9 days.[11-13]

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have been used in treating COVID-19 infection with the following actions: (1) immunomodulatory effects through inhibition of cytokine production. It can inhibit TLR-7 and TLR-9 signaling pathway and decrease the secretion of proinflamatory cytokines (IL-6, TNF-α, IL-1 and IFN-γ); (2) impairing lysosomal and autophagosome functions and subsequently immune activation; (3) inhibition of proteolytic processing and endosomal acidifation; (4) antiviral effects including impairment of viral replication,

interference with posttranslational modification of viral proteins, and inhibition of binding of viral particle to cellular receptors and (5) blocking virus-cell fusion and interference with glycosylation of SARS-CoV and ACE2 cellular receptors. The recommended dosage for Chloroquine is as follows : If the body weight is more than 50 kg, 500 mg twice daily is given for 7 days coarse of treatment. For body weight less than 50 kg, 500 mg twice daily is given for the first second days, followed by 500 mg once daily on the third to seventh days. For hydroxychloroquine the recommendation dosage is 400 mg given twice daily for the first day, followed by 200 mg twice daily for another 6 days.[11,13]

Azithromycin

Azithromycin is a macrolide antibiotic that has several actions including: (1) antimicrobial activity against Gram positive and Gram negative bacterial as well as atypical pathogens; (2) anti-inflamatory activity as it has been shown to reduce the blood levels of proinflamatory cytokines and chemokines; (3) immunomodulatory actions; and (4) antiviral activity as it has been shown to have in vitro activity against Zika and Ebola viruses. In pateints with COVID-19 infections, several studies have shown efficacy of azithromycin particularly when given in combination with chloroquine or hydroxychloroquine. The recommended dose of azithromycin is 500 mg once daily for 7 days.[11-13]

Corticosteroids

Corticosteroids are useful in the treating of a cytokine storm. Indication for corticosteroids treatment are acute hypoxemic respiratory failure, requirement for mechanical ventilation and another accepted indication for example COVID patients with asthma or COPD exacerbation. Another indication to administer corticosteroids includes a severe and critical clinical state, persistent fever (>39 ^{0}C), rapid deterioration suggested by CT-scan findings (more than 50% of the infected area on CT-scan images within 48 hours), plasma concentration of inflamatory cytokine, such as IL-6 $\geq$ 5 times above the upper limit of normal and patients not responding to anti IL-6 treatment. Dexamethasone 6 mg

daily for 10 days is strongly recommended based on RECOVERY trial. The median duration of steroids treatment in that study was only 7 days. Therefore if patients are already improving, the corticosteroids treatment may be safe to stop prior to 10 days. Higher doses of corticosteroids (dexamethasone 10-20 mg daily or equivalent doses of methylprednisolone) could be considered in patients with severe ARDS. If higher dose corticosteroids are used, the dose may be reduced to 6 mg dexamethasone daily or equivalent as soon as improvement occurs. Dexamethasone has a long biological half-life with its auto-tapper property and thereby prevent rebound inflammation.[1]

Venous Thromboembolism (VTE) Prophylaxis

Most patients with cytokine storm due to COVID-19 infection seem to be extremely hypercoagulable. This would support a potential role for VTE prophylaxis in COVID-19 infection. Enoxaparin 30 SC mg bid is suggested as preferred dose for VTE prophylaxis in critically ill patients with COVID-19. Enoxaparin 30 mg SC bid should also be considered for VTE prophylaxis in hospitalized ward-based patients. Higher doses of anticoagulant prophylaxis (enoxaparin 0.5 mg/kg BW SC bid) may be considered in patients with moderately elevated D-dimer (1500 ng/ml) and for patients with weight above 100 kg or BMI above 40 kg/m^2. Check an Xa level four hours after the third dose, targeting a level of 0.5-0.8 IU/ml.[1]

Antibiotic Treatment

For patiens with severe disease, early and appropriate empiric antimicrobial therapy should be based on the clinical diagnosis, local epidemiology and susceptibility data and national treatment guideline. Antibiotic should be given as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Empiric antibiotic therapy should be de-escalated on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching of intravenous to oral route of administration and provide targeted treatment based on microbiologic results.[1]

IL-6 Inhibitor

Tocilizumab is an IL-6 receptor inhibitor, which acts to interrupt IL-6 signals to immune effector cells, hence decreases the immune activation and alleviates the inflammatory processes. The recommended dose is 4-8 mg/kg BW. The recommended dose is 400 mg with 0,9% saline diluted to 100 ml. The infusion time is more than 60 minutes. For patients with poor efficacy of the first dose, an additional dose can be given with the same as initial dose after 12 hours. No more than 2 doses should be given. Maximum single dose is 800 mg.[11-13]

Intravenous Immunoglobulins (IVIG)

Intravenous immunoglobulins is a blood preparation isolated and concentrated from healthy donors consisting of over 95% of IgG and trace amounts of IgM or IgA. Potential antiinflamatory and immunomodulatory mechanisms of high-dose IVIG therapy are by neutralization of pathogenic antigens through the F(ab)'2-mediated mechanisms, immunomodulatory effects on endothelial cells, innate and adaptive immune cell through Fc-mediated mechanisms and neutralization of endogenous antigen including proinflamatory cytokines, chemokine and complement fragment. The suggested dose of IVIG is 0.3 - 0.5 g/kg BW/day for five days. Most of the research concluded immunoglobulin administration is effective and tolerable, but some also reported side effects occurring after the drug administration.[13-16]

Convalescent Plasma

Curently, convalescent plasma has been added to the existing treatments in patients who were unresponsive to the existing protocol. The efficacy of convalescent plasma would be improved with correct indication and timing. Theoretically, convalescent plasma is suitable to treat the disease in initial symptomatic phase.[17] The decision for the treatment of COVID-19 patients with convalescent plasma should be approved by a critical care specialist. This treatment is recommended to the confirmed case (positive result with PCR-test) or probable case (clinical/radiological evidence compatible with COVID-19, but PCR-test result not yet available), patients with COVID-19 who are

above 18 years old within the first 14 days of the disease and 7 - 19 days after the symptoms start. The recommended minimum dose for one patients is one unit (200 ml per unit) convalescent plasma. Second unit can be administered 48 hours following the completion the transfusion of the first unit of convalescent plasma and can be administered up to maximum of 3 units (600 ml). The decision for total dose is taken by the physician in charge and based on the clinical findings to avoid volume overload in patients who are instable in term of cardiopulmonary functions. Neutralizing antibodies (NAbs) are crucial in virus clearance and have been considered essential in protecting against viral disease. Antiviral effects of NAbs IgG and IgM are the main isotypes, although IgA may be also important particularly in mucosal viral infections. Passive immunity driven by convalescent plasma therapy can provide these NAbs that restrain the infection. The efficacy of this therapy has been associated with the concentration of NAbs in plasma from recovered donors. Immunomodulation is another possible action of convalescent plasma by controlling an overreactive immune system. The benefit of convalescent plasma therapy is greater when it is used in a timely manner in the early viremic phase as its main action is through direct neutralization of the virus, whereas the use of IVIG administration may be usefull even in a more tardive phase as its principal mechanism is to counteract the deleterious effects of the dysregulated immune respons.[15-18]

Mesenchymal Stem Cell Therapies

Mesenchymal stem cell (MSC) and their secretory products in the treatment of severe COVID-19 infections have the following beneficial effects therapies : (1) Suppression of viral replication, viral shedding and virus-induced damage to lung epithelial cells; (2) enhancement of the generation of regulatory T-cells that are suppressed by COVID-19; (3) MSCs modulate the proliferation and activation of naïve and effector T-cells, NKCs and mononuclear cells; (4) MSCs prevent the formation of NETs that may have deletetious effects in the patients with COVID-19 pneumonia; (5) MSCs can inhibit

the cytokine storm induced by COVID-19; (6) secretomes of MSCs have antiviral, antibacterial and even analgesic effects; (7) reduction in pulmonary edema associated with ARDS in COVID-19; (8) enhancement of tissue regeneration and promotion of endogenous repair and healing in ALI induced by COVID-19. MSCs at dose of 1 x 106 cells/kg body weight, administered intravenously. MSC are suspended in 100 ml saline and injected over 40 minutes.[19-20]

Oxygen Treatment

In selected patients with mild ARDS, high flow nasal canule (HFNO), non-invasive ventilation-continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) can be used. Compared with standard oxygen therapy, HFNO may reduce the need for intubation. Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0. Patients receiving HFNO or NIV should be in monitored setting and care for by personnel experienced with HFNO and or NIV and capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after 1 hour. In this case intubation should not be delayed. Patients with hypercapnia, haemodinamic instability, multiorgan failure or with abnormal mental status should not receive HFNO. High flow nasal canule and NIV should be used in isolation room with airborne precautions. If HFNO and CPAP are not available, oxygen is delivered via face mask with reservoir bag (flow rates of 10-15 L/min, which is tipically the minimum flow required to maintain bag inflation with FiO2 0.60-0.95). Intubated patients should use low tidal volume (4-8 ml/kg predicted body weight and lower inspiratory pressure /plateau pressure < 30 cmH2O). In severe ARDS (PaO2/FiO2 < 150) prone ventilation for 12-16 hours per day is recommended. In moderate or severe ARDS a higher positive end-expiratory pressure (PEEP) is suggested. Titration of the PEEP is performed individualized with monitoring for beneficial and harmful effect. In patients with moderate-severe ARDS (PaO2/FiO2 < 150), neuromuscular blockade by continuous infusion should not be routinely used. Avoid disconnecting the patien from the ventilator wich results in loss of PEEP,

atelectasis and increased risk of infection of health care workers. Consider to refer patients who have refractory hypoxaemia (PaO2/FiO2 < 50 mmHg for 3 hours or < 80 mmHg for > 6 hours) despite lung protective ventilation to access treatment with extracorporeal membrane oxygenation (ECMO). Extracorporeal membrane oxygenation is a resource-intensive technique restricted to specialized centers, and it remain an extremely limited resource. Therefore its use as a rescue should be reserved for carefully selecterd patiens.[1]

PROGNOSIS

In general, the prognosis of ARDS in COVID-19 infection is depend the severity of the disease. Patients with mild ARDS usually have favorable outcome with early medical and supportive treatment. The condition of the patients may be reversible if administered therapy showed an acceptable response. However, ARDS due to cytokine storm can be severe and life-threatening, leading to multi-organ failures even with agresif medical treatment. Neurologic disorders occurring in this syndrome may be reversible but can indicate a dangerous complication of cerebral edema or brain stem death.[9]

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