Treatment of the Cytokine Storm in COVID-19

Burcin HALACLI[1] , Arzu TOPELI[1]

[1]Hacettepe University, Department of Internal Medicine, Division of Intensive Care Medicine, Ankara, Turkey

Corresponding Author: Burcin Halacli

E mail: burcin.halacli@yahoo.com

ABSTRACT

Cytokine storm has been proposed as the basis of the pathophysiological process of COVID-19 caused by SARS-CoV-2. Cytokine storm, generally known as excessive or uncontrolled release of especially pro-inflammatory cytokines, occurs due to several infectious and non-infectious causes. For this reason, many treatment options that have been tried before have been applied for COVID-19 patients as well. Although there is not a proven treatment so far, there are some promising agents. Hereby, we tried to emphasize some anti-cytokine drug and treatment modalities for COVID-19 patients.

Key words: SARS-CoV-2, Corona Virus, Anti-Cytokine, Hemophagocytic Lymphohistiocytosis, Macrophage-Activation Syndrome

Introduction

Corona virus disease of 2019 (COVID-19) caused by severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) seems to be the biggest pandemic affecting all layers of society in the world including health-care systems that we have encountered in this century. Although most patients have mild to moderate disease with respiratory symptoms such as fever, cough, myalgia and fatigue, approximately 15% of cases may progress to severe pneumonia, and 5% of cases may end with acute respiratory distress syndrome (ARDS), septic shock and multiple organ failure requiring intensive care (1, 2). Although many anti-viral agents have been tried for COVID-19, unfortunately there is no proven treatment modality so far. In the light of the steadily learned knowledge about immunopathology of especially severe phenotypes of COVID-19, the use of some therapies other than anti-viral drugs have become popular (3). In this review article, we aimed to summarize possible immunomodulatory treatment options that might be utilized in the pathophysiological condition so-called "cytokine storm" which might be observed during COVID-19.

Cytokine storm

Cytokine storm (CS) is an exaggerated systemic inflammatory response with an evident expansion of large number of cytokines seen during the course of wide spectrum of diseases, conditions or medications like infections, sepsis, organ transplantation, autoimmune diseases or immune-related therapy like Chimeric Antigen Receptor-T (CAR-T) cell therapy for some malignancies (4-5). Viral infections have been one of the major stimulators of CS. Innate and adaptive immunity can be urged in an uncontrolled way by SARS-CoV-2 infection, when virus binds to alveolar epithelium and substantially may cause tissue damage. In COVID-19 patients, there is T-helper 1 (Th1) activation in which the inflammatory response is predominant, but cytokines that suppress the inflammatory response such as interleukin-4 (IL-4) and IL-10 can also be released from T-helper 2 (Th2) cells (1). Severity of the disease has been shown to be associated with high serum levels of IL-2 receptor (IL-2R) and IL-6 in patients with COVID-19 (6). One study revealed that high levels of IL-6 were more frequent in COVID-19 patients with severe disease compared to those with mild disease (76 vs 30%) (7). In another study (1), patients

admitted to intensive care unit (ICU) had higher serum levels of granulocyte colony-stimulating factor, interferon-gamma-induced protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1A and tumour necrosis factor-α (TNF-α) in comparison to COVID-19 patients from general wards. This could be interpreted that there might be a correlation between level of CS and disease severity.

CS has a wide range umbrella that contains several critically-ill situations. One of the most known this group is hemophagocytic lymphohistiocytosis (HLH). HLH is a life threating uncontrolled condition characterized by severe CS. Although our information about HLH is a familial or primary form belonging to the pediatric age group, we are encountering an increasingly common form in adulthood what we call secondary HLH (sHLH). sHLH, which often develops due to infections, is defined as macrophage activation syndrome (MAS) in the case of autoimmune diseases. Clinical and laboratory signs and symptoms include severe elevation in acute phase parameters such as C-Reactive Protein (CRP), persistent fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, elevation of aspartate aminotransferase (AST) and ferritin level, presence of hemophagocytosis in bone marrow or other tissues. This extremely severe and rare condition is seen in approximately 5% of critically-ill patients (8), and these patients should be followed closely and their treatment should be continued in ICU (9). COVID-19 might also theoretically cause this condition, but there is no high level of evidence in the literature regarding its frequency and definitive treatment. Since 5-10% of COVID-19 patients may be critically-ill, sHLH or CS might be observed in 1% of patients at most, requiring treatment. The diagnostic algorithms and criteria developed for this clinical picture are presented at Table 1 and 2 (10-11). sHLH/MAS related to COVID-19 pneumonia has different immunopathology which is generally only lung-based, organomegaly and lymphadenopathy are absent (12). Severe COVID-19 patients often presented with fever, typical laboratory findings and ARDS. Manifestations of hyperinflammation are cytopenias as thrombocytopenia and lymphopenia, coagulopathy as low platelet and fibrinogen and high D-dimer levels, tissue damage as increased lactate dehydrogenase (LDH), AST and alanine aminotransferase levels (ALT), and macrophage/hepatocyte activation as elevated ferritin levels. But, ferritin is not detected as high as seen in HLH or MAS (13).

Table 1. Histiocyte Society Hemophagocytic Lymphohistiocytosis Diagnostic Criteria (10)

Having at least 5 of the following:
1. Body temperature > 38.5 °C 2. At least 2 cytopenia in the peripheral blood (Haemoglobin < 9 g/dL, Neutrophil < 1000 / mm³, Platelet < 100.000 /mm³) 3. Splenomegaly 4. Fasting triglyceride ≥ 265 mg/dL and/or fibrinogen < 150 mg/dL 5. Ferritin ≥ 500 mcg/L 6. Low NK activity (according to laboratory reference) 7. Increased soluble IL-2 receptor activity (based on adult value) 8. Hemophagocytosis in the bone marrow or other tissues

NK: Natural Killer cell; **IL:** Interleukin

Potential implications of immunomodulatory therapies

Although there is still insufficient evidence, several anti-viral therapies are used to treat COVID-19 all over the world. Considering the pathogenesis of CS in severe COVID-19 cases, anti-inflammatory drugs are considered as treatment options. It has been postulated that there is a 5-7 days period between diagnosis and progression to severe form (7). Thus, early utilization of immunomodulatory therapies was suggested in order to prevent disease progression and reduce morbidity and mortality in advance. On the other hand, treatment modality, risks and benefits, duration of treatment, etc. are unknown. Furthermore, some immunomodulatory therapies bring risk of elimination or suppression of inflammatory cytokines necessary for virus clearance (14).

Table 2. H Score for Hemophagocytic Lymphohistiocytosis Diagnosis (11)

	Score
Body temperature (°C)	
<38.4	0
38.4-39.4	33
>39.4	49
Organomegaly	
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Cytopenia (Haemoglobin ≤ 9,2 g/dL; Leukocyte < 5000 /mm³, Platelet < 110.000 /mm³)	
One lineage	0
Two lineages	24
Three lineages	34
Triglyceride (mg/dL)	
< 133	0
133-354	44
> 354	64
Fibrinojen (mg/dL)	
> 250	0
≤ 250	30
Ferritin (mcg/L)	
< 2000	0
2000-6000	35
> 6000	50
AST (U/L)	
< 30	0
≥ 30	19
Hemophagocytosis in bone marrow (not mandatory)	
No	0
Yes	35
Immunosuppression (HIV, chronic steroid and another immunosuppressive drug use ...)	
No	0
Yes	18
H score> 169 for diagnosis has a high diagnostic value.	

AST: Aspartate Aminotransferase; **HIV:** Human Immunodefficiency Virus

Glucocorticoids

Glucocorticoids could reduce fever and improve oxygenation by suppressing systemic and lung inflammation. It has been used during previous coronavirus infections as SARS and Middle East Respiratory Syndrome (MERS) for immunomodulation therapy (14). However, current evidence suggests that routine use of steroids for COVID-19 patients with viral pneumonia or ARDS is not recommended unless patient has refractory septic shock or chronic obstructive lung disease acute exacerbation (12). Corticosteroids might delay virus clearance and increase viral load (15). According to Surviving Sepsis Campaign (16)-a joint initiative of European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM), it is recommended that only short-term (≤7 days) and low doses of steroids (≤ 0.5–1 mg/ kg daily of methylprednisolone or equivalent) can be used in selected SARS-CoV-2 patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic conditions and in terms of septic shock with critically-ill related corticosteroid insufficiency. High dose or pulse steroid is not recommended, as well (17).

IL-6 antagonists

Among the immunomodulatory therapies, probably the most discussed agent is the IL-6 receptor antagonists. IL-6 is derived from T and endothelial cells, fibroblasts, macrophages and monocytes. Its major functions are proliferation and differentiation of B cells leading to production of antibodies, induction of cytotoxic activity of T cells, induction of acute phase protein production from liver and differentiation of hematopoietic stem cells. There is no clear evidence on the role of IL-6 in the pathogenesis of SARS-CoV-2. IL-6 has a potential of anti-viral ability. If the IL-6R is blocked in early phase of COVID-19, It should be noted that viral defence especially in type-2 pneumocytes could be deteriorated (18). The well-known member of this group is tocilizumab, an anti-human recombinant monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors and is mainly used in rheumatoid arthritis treatment (19). Food and Drug Administration (FDA) approved its use in CS due to CAR-T cell therapy (20). Therefore, it has been contemplated to be utilized for CS seen in COVID-19. In a case series of twenty COVID-19 patients published from China who were administered tocilizumab, it was reported that in 19 patients' lung infiltrations were completely eliminated, oxygen treatment was reduced in 15 patients, CRP levels decreased in 17 of the patients and lymphocyte values were normalized in 11 of cases (21). There are currently several ongoing multicentre randomized controlled trials (RCTs) with tocilizumab in the process of patient recruitment (clinical.trials.gov). It was reported that tocilizumab has a positive effect on COVID-19 related CS (18). Besides clinical findings, COVID-19 patients evaluated as sHLH, Tocilizumab can be administered at a dose of 4-8 mg/kg (up to 800 mg). Depending on the severity of the patient's findings, it can be administered as 400 mg or 800 mg IV. When the first dose is made as 400 mg, considering the changes in clinical and laboratory findings, a dose of 200-400 mg can be repeated within 12-24 hours. It should not be used in pregnancy, neutropenia (<500/mm³), active tuberculosis, active hepatitis B or C infection, in the presence of allergy and hypersensitivity. Liver tests and platelet counts should be monitored and patients with history of diverticulitis should be closely monitored for gastrointestinal

perforation (22). Another IL-6R antagonist is sarilumab which is being investigated in RCTs and still recruiting patients right now (clinical.trials.gov).

IL-1 antagonists

IL-1, which is a cytokine secreted from monocytes and tissue macrophages, plays an important role for the inflammatory response. Blocking IL-1R may suppress this process. Anakinra, which is commercially available as an IL-1R antagonist that blocks activity of IL-1α and IL-1β and is mainly utilized for adult-onset Still's disease, systemic-onset juvenile idiopathic arthritis and familial Mediterranean fever dose of 100 mg/day subcutaneously in adult patients (23). It is thought to be useful in patients with severe COVID-19, since anakinra has also been shown to improve survival in sepsis in a subgroup analysis of a phase 3 RCT (24). The effectiveness of anakinra on COVID-19 patients is currently being investigated by a RCT (clinical.trials.gov). In a recent retrospective study (25), high dose IV anakinra has been tried for COVID-19 patients (n=29) with ARDS and high CRP and ferritin levels who were managed by non-invasive ventilation out of ICU. It was shown that high dose IV anakinra was safe and clinical development was obtained in 72% of study group.

Intravenous Immunoglobulin (IVIG)

Since IVIG has been used in immunodeficiencies and severe or refractory autoimmune diseases, high doses (> 0.5 g/kg/day) could be used for the management of CS due to its anti-inflammatory and immunomodulating functions (26). Although there is not much evidence for its use in COVID-19, IVIG seems to be safe regarding impairment of viral clearance (13). A study by Chen et al. (27) reported that 27% of 99 Wuhan patients with COVID-19 had received IVIG treatment. An RCT has been initiated in terms of IVIG treatment for severe COVID-19 patients (clinical. trials.gov). However, transfusion related acute lung injury and thrombotic events related to IVIG treatment could be encountered with 1–16.9% incidence (28).

Convalescent Plasma

Convalescent plasma (CP) of immunised people for treating severe infections has been used for a long time. It has also been proposed to treat COVID-19. However, antibody dependent enhancement (ADE) of SARS-CoV-2 is possible. People who recovered from COVID-19 have non-neutralizing antibodies in their plasma which may bind to the virus, enhancing its entry into host cells, and sometimes also its replication. It may induce complement activation leading to vascular injury and cause systemic necrotising vasculitis, disseminated intravascular coagulation, induction of CS and sustained lymphopenia, which were reported in ADE phenomenon (29). A case series with five COVID-19 patients showed that use of CP could be safe and effective (30).

Janus Kinase (JAK) inhibitors

JAK pathway has a dual function in COVID-19 pathophysiology which are inflammation and virus entry into the cells. Ruxolitinib a JAK 1 and 2 inhibitor is currently an available agent of this family approved by FDA for the treatment of primary myelofibrosis, polycythemia vera and rheumatoid arthritis. It has been tested for

HLH in a murine model and resulted in a decline in serum IL-6 and TNF-α levels (31). SARS-CoV-2 invades cells by endocytosis, binding to anjiotensin converting enzyme 2 (ACE2) receptors on cells. Adaptor protein complex 2 (AP2)-associated protein kinase 1 (AAK1) is one of the accepted promoters of this endocytosis. Baricitinib, a JAK inhibitor as well as an AAK1 inhibitor may prevent this entry and by this way it blocks virus shedding. On the other hand, JAK inhibitors may suppress some inflammatory cytokines such as INF-a which has also antiviral activities (32). That's why we need more studies in order to clarify the exact effects of JAK inhibitors. There are ongoing trials on the use of JAK inhibitors for COVID-19, as well (clinical.trials.gov).

Other anti-inflammatory or immunomodulatory agents or therapies

There are many other agents or therapies that were studied to have anti-inflammatory or immunomodulatory activities. Interferons were thought to be beneficial in early phase of SARS-CoV and MERS-CoV infections by declining viral load and improving clinical symptoms. However, mortality rates were not improved (33). As a potential precipitator of inflammation, inhibition of TNF was studied in an animal model for SARS-CoV infection which concluded with positive results (34). But, there is not any recommendation for COVID-19 patients so far. Calcineurin inhibitors (cyclosporine and tacrolimus) may have inhibitory role for viral replication that was revealed in experimental studies of SARS-CoV (35). Anti-malarials (chloroquine and hydroxychloroquine) have an activity of supressing TNF and IL-6 production that was reported in COVID-19 patients (36). Anticoagulants (heparin and low molecular weight heparin) may protect endothelial cells from apoptosis and prevent complement activation due to TNF-α induction (37). Statins inhibit production of pro-inflammatory cytokines and T-cell activation by blocking of major histocompatibility complex II (MHC-II) expression which brings the potential pleiotropic effects to be used as an additive therapeutic agent (38). Mesenchymal stem cells (MSC) has been proposed to be utilised for COVID-19 patients with severe ARDS due to not only renewal of lung tissues, but also have anti-inflammatory functions by inactivation of T lymphocytes and macrophages, and promoting their differentiation into regulatory T cell (Treg) subsets which have strong anti-inflammatory capabilities (39). Blood purification treatments like cytokine adsorption, therapeutic plasma exchange and continuous renal replacement therapy have been used for the purpose of removing cytokines and chemokines which were accused to cause CS in different aetiologies (40-41).

Conclusion

Preliminary results of observational studies for severe COVID-19 patients suggested that CS is the underlying basic pathophysiology which may be encountered during early phase of disease process. There are more than enough drugs and treatment modalities that have been tried so far for CS related to SARS-CoV-2. It should not be forgotten that the benefits of any of these therapies have not been scientifically proven. All applied treatments have "double-edged sword" results. Therefore, the decision should be made by thinking on the basis of the patient at the point of application and the principle of "primum non nocere" should not be abandoned.

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