Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [2] January, 2023: 90-97

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Role of Anti Cytokine Interventions in COVID 19: SARS COV-2

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ABSTRACT
Coronavirus disease-19 (COVID-19), which emerged from China during December 2019 and showed a drastic spread around the world forcing the physicians and scientists to take on extraordinary challenges. Clinical investigations proposed that cytokine and interferon's production in SARSCoV-2 has shown strong up-regulation and induced lung damage amongCOVID-19 patients. Cytokines are crucial to the pathophysiology of COVID-19; while some of them are detrimental such as IL-1β, IL-6, IFN and TNF –α and hence it is called as cytokine storm. the present study compiles the data regarding the changes released of various cytokines expression in patients with COVID-19. The role of cytokines and their impact on outcomes in this disease will help the design of more successful approaches to COVID-19 management.
Keywords: COVID 19, SARSCoV-2, Cytokines, Interleukins, Interferons.

Received 21.08.2022 Revised 14.11.2022 Accepted 10.12.2022

INTRODUCTION

Severe acute respiratory syndrome corona virus (SARS-CoV-2) commonly known as COVID-19 first appeared in December 2019 in Wuhan city, China and declared as pandemic by WHO[1]More than 4 million people were affected and 278,000 deaths were reported as of 11th May 2020 worldwide. Most of these patients, were severely ill and deceased, did not show serious symptoms in the early stages of illness. Only few patients showed mild fever, cough, shortness of breath and discomfort to breathe freely which in resulted in pneumonia [2][3][4]and neurological symptoms [5].

Furthermore, it was determined that the disease progression and mortality were closely related with the increased levels of cytokine release in critically ill patients which is known as cytokine storm[6]. Cytokine storm exhibited a pivotal role for the rapid progression of COVID-19.Accordingly, cytokine storm diagnosis is considered as a significant aspect in the treatment of seriously infected COVID 19 patients. In individuals who were affected with cytokine storm, physicians will focus on attenuates or eliminates the up regulated proinflammatory cytokines like IL-6 and TNF-α by hemoperfusion[7]. Elevated levels of cytokines will lead to edema, failure in gas exchange, acute disorders occur in heart and lungs along with secondary infection [8].

Elevated levels of cytokines and chemokines like IL-6, interleukins-10, TNF-α were observed in the COVID- 19 patients. Thus, Intensive Care Unit (ICU's) patients were reported with increasing the levels of interleukins-1, interleukins-7, interleukins-10, "macrophage colony stimulating factor-(M-CSF), "granulocyte colony-stimulating factor", "granulocyte macrophage colony stimulating factor (GM-CSF)", "10 kD interferongamma-induced protein (IP-10)", "monocyte chemoattractant protein-1 (MCP-1)", "macrophage inflammatory protein 1-α" in the serum[9,10]. Analysis of the factors that underlie pathophysiological is essential of this COVID 19 pandemic disease and some cytokines seems to play a vital role. The objective of the present work is to review the role of pro-inflammatory cytokines and its antagonist in novel corona virus 2019.

SARS- CoV 2- Cytokine storm

Cytokines are chemical messengers intended for immunologic responses which can trigger both innate and adaptive responses. Dysregulated and overreacting immune status can damage human immune system. The pertinent evidence from severely sick SARS CoV-2 infected individuals shows that proinflammatory cytokines interleukin (IL), interferon (IFN), tumor necrosis factor (TNF), colony stimulating factor (CSF), chemokine and growth factor play an important role in pathogenesis. Various cytokines will be released due to the invasion of microbes such as bacteria and viruses into the human body and tend to alter the immune system[11][12]. Several cytokines are secreted, which is also called as "Cytokine Release Syndrome" (CRS), is directly associated to the clinical symptom of HCoV. For instance, signs such as fever, chills, headache, and dizziness are caused possibly due to interferon gamma; Blood vessel leakage, heart failure, pulmonary lesions and protein synthesis in acute phase[13] are due to TNF-α and disseminated intravascular thrombosis, leakage in blood vessel, complement system activation and clotting cascade are observed due to interleukin-6[14][15].Hence, it is noteworthy to mention that interleukin-6 is responsible to produce cardiomyopathy by causing heart attack which is common symptom in CRS patients [16]. Additionally, endothelial cell activation may also be one of the phenomenal characteristics in serious CRS. Due to the over activation of endothelial cell dysfunctions which in turn cause, "capillary leakage", "hypotension", and "coagulopathy"[17]. In SARS CoV-2, there is a close relationship between pro-inflammatory cytokines and evolution and progression of acute respiratory distress syndrome (ARDS)[18]. Patients with ARDS show a significant increase in cytokines level in the serum, which is evidenced in the death rate [19]. The extra-pulmonary multiple organ failures evidenced by the elevated levels of liver enzymes and creatinine which in turn is caused by the increased levels of pro-inflammatory cytokines in the serum.

In short, the novel form of coronavirus triggers an inflammatory infection in patients with cytokine storm. Several research findings give a detailed account in words of increased levels pro-inflammatory cytokines and chemokines. The cytokine storm develops into ARDS or multi-organ extrapulmonary insufficiency and is the critical factor that exacerbates COVID-19, or even causes death.Therefore, the treatment for SARS CoV-2 infected individuals is to reduce the inflammatory reaction through immunomodulation is considered as an effective method of treatment and also helps in monitoring and the prognosis of HCoV infection [20][21][22]. (Table No.1).

Interleukin-1 and its antagonists in SARS CoV-2

Interleukin-1is mainly involved in the inflammatory response due to infection and as a result, its monocytes and macrophages are activated[23][24]. It is reported that SARS-CoV-2 acts on IL1β activation and maturation, which further activates other pro-inflammatory cytokines, for example IL6 and TNF-alpha[25][26][27]. One research finding proposed that high levels of IL-1α were observed in COVID-19 patients who were closely linked to lung injury[28]. Symptoms including hypercoagulation and disseminated intravascular coagulation have been detected in the COVID-19 patients associated with increased level interleukin-1[29].It was also shown that increased levels of IL-1β is essential for ARDS[30]and Hemophagocytic lymphohistiocytosis (HLH)[31]. Both juvenile as well as in Adults Still's disease, HLH is a common complication with pathophysiology due to very high levels IL-1β[32]. Hence, to avoid the cytokine storm IL-1 inhibitors have been employed [14], [33]Anakinra, an antagonist of IL-1β, may be used to treat the cytokine storm triggered by infection. It has been treated effectively in the condition of HLH[34] cryopyrinopathies[35] and Still's disease[36]. IL-1 β antagonist anakinra was given to patients with severe sepsis accompanied with reHLH had shown remarkable improvement without producing adverse effect in Phase –III randomized trial were documented [37]. It is therefore considered as a safe drug for SARS CoV-2 patients having symptoms of cytokine storm. Canakinumab is an monoclonal anti-IL-1β antibody administered by SC injection at the dose of 150mg which attains peak serum concentration in a week [38]. Another molecule, Rilonacept is a recombinant soluble IL-1 receptor developed for IL-1 blockade at a recommended dose of 2.2 mg/kg [39]. Till date, the use of Canakinumab or Rilonacept to SARS CoV-2 infections has not yet been reported.

Interleukin-6 and its antagonists in SARS CoV-2

Interleukin-6 played a pivotal role in immune response related inflammation, formation of blood cells in mesenchymal stem cells. Interleukin-6 moves to the hepatic tissues during inflammation in the beginning stage and also trigger the other proteinaceous substance like "C-reactive proteins" (CRP), "serum amyloid A" (SAA), "fibrinogens", "haptoglobins"and "alpha1-antitrypsin" and decrease the production of "albumin", "fibronectin", and "transferrin[40]. Activation of Janus kinase (JAK) signal binding with cis transmembrane and soluble form trans signaling of IL-6Rare associated with membrane bound gp-130 by IL-6. Increased level of IL-6 signaling causes vascular endothelial growth factor (VEGF) expression[14]that in turn lead to organ damage such as] and decrease in myocardial contraction[16].In SARS CoV-2 patients it has been observed that IL-6 levels and CRP are elevated which related to a weak

prediction of the disease[41, 42].Many pro -inflammatory markers including interleukin-6, interleukin-10, interleukin-2, Tumor necrosis factor and interferon gamma were significantly increased in SARS CoV-2 patients and found the reduction in the lymphocyte count with severe pneumonia. Among the cytokines, an increase in the level of IL-6 is considered as the major cause of cytokine storm was well documented in several studies[43][44][45][46][47].Up-regulation of Il-6 level could induce the B and T lymphocytes differentiation[48]. Generation of GM-CSF and pathogenic Th 1 cells were activated rapidly from the CD 4+Th which progresses into inflammation in the SARS CoV-2 patients. Thus, the abnormally increased levels of immune cells possibly enter into pulmonary circulation and damage the normal functions of pulmonary cells leads to mortality[49].Notably, IL-6 play an important role as a mediator of CRS and as a result, drugs intended to block cytokine storm are mediated by IL-6.

In hospitalized COVID19, as IL-6 levels correlate with seriousness of the disease, therefore anti-IL-6 treatment was one of the initial methods for treating the patients as examined during the Pandemic[50][51][52][53]. The use of monoclonal antibody, Tocilizumab, a US FDA approved potent IL-6 antagonist for the treatment of cytokine storm, in addition to "Rheumatoid arthritis" "idiopathic arthritis" and "giant cell arthritis". Severe lung disease and extensive bilateral lung lesions associated with IL-6 increased level patients have been treated with Tocilizumab in clinical studies at China. Bizzarri *et al*., had also described the polyol myo-inositol drug to lower levels of IL-6 and also reduce the risk of Cytokine Storm[54]. Additionally, combination of hydroxychloroquine with azithromycin was capable enough to block the increased amounts of IL-6 and TNF-α in SARS CoV-2 patients[55].Interestingly, Chloroquine also showed good potential towards the inhibition of IL-6 and TNF-α levels among the COVID-19 patient samples[56]. Blood purification technique is also effective to eliminate most of the cytokines including IL-6[57].Heparin, an established anticoagulant drug accompanied with anti-inflammatory properties also found to lower IL-6 levels[58,59]. Tanaka et al, carried out a retrospective study on patients with COVID-19 treated with low molecular weight heparin (LMWH) and observed a reduction of IL-6 levels[60]. LMWH playa dual role in the COVID-CRS to reduce both IL-6 triggered inflammation and also reduce the clotting risk cascade.Nevertheless, the severe risks of tocilizumab that include a slight chance of perforation in the bowel, hepatic acute insufficiency and jaw osteonecrosis were also reported[61]. In addition, few studies revealed that hypertriglyceridemia and candidaemia were reported among COVID-19 patients who were treated with tocilizumab infusion[62],[63].

Role of TNF- α and its antagonists in SARS CoV-2

TNF-α comes from different types of cells, such as monocytes, macrophagesand T cells. It regulates the infectious disease, malignant tumours and inflammatory processes that trigger a cytokine storm[64]. There are appealing ways to control cytokine storm. The serum TNF-α level has been shown to be increase in SARS CoV-2 patients compared with other severe illness[8,42,51].In a sample of 522 patients, the reverse relation between TNF-α and T-cell count was found with COVID-19 were reported[65]. A survey was conducted from a number of independent studies of the same subjects affected with SARS CoV-2 showed that inhibition of TNF-α has significantly showed beneficial effects in the patients having sepsis[66] and atherosclerosis[67]. *In vivo* studies proposed that TNFs played a significant role in acute lung infection and T cell impairment in mice treated with SARS CoV. In addition, neutralization or loss of TNF receptor function provides defense against morbidity and mortality caused by SARS-CoV[68],[69]. Conversely, Wan *et al.,*proposed normal TNF α levels in SARS CoV-2 patients[70]. Previous research findings suggests that treatment of certolizumab, an anti TNF- α antibody, could have a potential benefit against SARS CoV-2 patients[71]. There are currently no suggested TNF blockers in the treatment of COVID-19 patients but efficacy of TNF blockers, requires further research

Role of IFNand its antagonists in SARS CoV-2.

Interferons (IFN) strengthen the immune system in various aspects; theyexhibit a lot of biological functions such as antiviral, antiproliferative, and immunomodulatory effects [72]. IFN-αβ restricts the replication of viruses and thus exacerbates diseases by enhancing the mononuclear macrophages and innate immune cells.Although a quick intervention to interferon has a protective effect on SARS-CoV affected rodents, later IFN-αβ signaling triggers immune response imbalance to SARS-CoV in the mammals. This observable fact states that scheduling of IFN therapy is important for the outcome of the illness[73].

IFN-γ processed by a wide range of lymphocytes cells including CD4 + cells CD8− T and B cells and natural killer cells. It can also be produced by monocytes, macrophages, dendritic cells and neutrophil granulocytes. IFN-γ takes an active participation in the activation in macrophage and antigen presenting cellsand mainly involved in anti-viral, anti-bacterial and in signal transduction. In COVID-19 patients, the serum interferon-gamma levels were found to be higher than in non-infected persons and thus suggested that increased levels of cytokines may be due to the result of Th1 and Th2 cell activation. In addition, several reports had shown that there were increased serum levels of IFN-γ in SARS-CoV or MERS patients

[8,74,75]. It is noteworthy that higher IFN-γ levels were correlated with higher rates of lung damage and viral load were documented[28].Emapalumab is a monoclonal antibody approved by US FDA focused on interferon γ and t has been treated for refractory, recurrent, or progressive primary HLH in both children and adults[76]. Reports were scanty about the use of emapalumab in adults, on secondary HLH. Recent reports suggested that in patients diagnosed with MERS-CoV, the mixture of Remdesivir and IFN β showed better anti-viral impact, compared to lopinavir and ritonavir[77]. Remdesivir and IFN β may also prove to be helpful in the treatment of SARS CoV-2[72],[78],[79].Interestingly, recent reports in the clinical trials had shown that the SARS CoV-2 patients who were treated with Remdesivir had reduced duration of stay in the intensive care unit.

IFN α and γ had shown partial effectiveness and inhibition of *in vivo* and *in vitro* replication of SARS-CoVeither alone or in combination with anti-viral agent. Interferon β shows potential antiviral efficacy with prophylactic protection[80].Thus, a safety and effectiveness testing may be worthy suggestion in human and recombinant IFNs in patients affected with SARS-CoV-2, alone or in combination with any other antiviral medication. .

Table 1: Involvement of cytokines in COVID 19 patients

Objectives studied	Symptoms/Biochemical observation	Implications
Clinical and epidemiological character of COVID 19 Lung disease	Fever, cough, shortness of breath muscle pain.	Most of the affected peoples had been exposed to market at Wuhan. Infected persons diagnosed with ARDS or died from organ failure[52].
Clinical symptoms between ICU and Non ICU patients with SARS CoV-2	Fever, cough, myalgia, dysnoea, Lymphopenia.	Elevated levels of cytokines such as IL-1, IL-7, Il-10 and TNF alpha were observed in ICU patients[8].
Treatment and prognosis of COVID 19 patients	Fever, cough, myalgia, decreased WBC count, lymphocytopenia.	Treated with IgG to severly affected patients. No benefit with steroidal medicaments. Increase risk of death related to aged and comorbities[9].
Cytokine storm syndrome in SARS CoV-2.	Increased Pro inflammatory cytokines including IL-2, IL-7, IL-6, TNF-α were observed in the plasma.	IL-6 antagonist tozulimab or Il-1 β antagonist anakinra helps to reduce the hyperinflammation in SARS CoV-2 patients[41].
Role of immune system and different cytokines in COVID 19	Increased levels of Cytokines.	Upregulation of Il-6 and IL-10 and downstream of CD4 + and CD 8+ levels were observed .It worsened the condition of the patients[46].
Relevant information about SARS CoV-2	Fever, dry cough, dysnoea, myalgia, headache, sore throat and diarrhea.	SARS CoV-2 is more infective than the SARS and MERS. Treated with asymptomatic treatment along with ventilation[81].
Epidemiological and immunological features of SARS CoV-2	Fever, dry cough, dysnoea.	Male are more affected than female. Aged peoples are more prone and death. Previous pathological conditions such as high BP, heart problems, pulmonary disease are more affected to SARS CoV-2. Finally,pulmonary lesions along with pro inflammatory cytokine storm[82].
Mode of vertical transmission of SARS CoV-2	Alteration in cytokines.	A newborn identified SARS-CoV-2 with IgM antibody, though negative to RT-PCRs[83].
Role of cytokine storm in patients with SARS CoV-2	Lymphopenia, Elevation in cytokines.	Increased levels of IL-6, IL-10 and TNF-α and decreased in interferon in CD4+ T cells[84].
Mortality rates in SARS CoV-2 patients	Increase levels of thromocytes, agranulocytes in WBC, Plasma protein including albumin, nitrogenous waste like urea, creatinine and myoglobin, CRP and IL-6.	Death rate may be due to aged people, comorbidities, secondary infections[85].
Cytokine release syndrome	Fever, hypoxia and shock.	Bichemical findings decrease the level of CD3, CD8 and natural killer cells.Increased level of IL-6. Treated with anti inflammatory drugs and ventilation[86].
Correlation between SARS CoV-2 and cytokine storm	Fever, cough, myalgia, lymphocytopenia.	MSC therapy showed effective in inhibits the T lymphocytes activation, macrophages and also suppresses the IL-1, Il-6, TNf-alpha[87].
Correlation between the pro inflammatory and pulmonary inflammation. Role of anti inflammatory drugs	Fever, Fibrosis.	Cytokines including IL- 37 and 38 inhibit the IL-1 and IL-6 has been observed[88].
Role of different cytokines in SARS CoV-2 patients	Increased levels of Cytokines.	Elevated levels of IP-10, MCP-3 and interleukin -1 alpha. These markers produced more severe and even death[89].
Transcription changes in lung fluid and blood cells.	Expression of cytokines.	Abnormal release of cytokines along with activation P53 signaling pathway [90].

CONCLUSION

It is observed that an immunological reaction caused by SARS-CoV2 infection instigates several pro inflammatory cytokines in the body. .This present study summarizes the findings regarding the role of cytokines in the onset of the infection in a comprehensive manner. Further, this study highlights on the effectiveness of various immunomodulators and cytokine antagonists in the initial stage playeda remarkable role in the cytokines storm and thus helps in reducing the severity and mortality of SARS CoV-2 patient.

ACKNOWLEDGEMENTS

The authors thank the management, B. S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, ChennaiThe authors further extends their gratitude to Dean, Crescent School of Pharmacy for his support and encouragement towards this work.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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CITATION OF THIS ARTICLE

Prakash Ramakrishnan, Sowmyalakshmi Venkataraman, Binoy Varghese Cheriyan. Role of Anti Cytokine Interventions in COVID 19: SARS COV-2. Bull. Env. Pharmacol. Life Sci., Vol 12[2] Jan 2023: 90-97.