Review Article **ISSN: 2349 – 7114**

Asian Journal of Research in Pharmaceutical Sciences and Biotechnology

Journal home page: www.ajrpsb.com

https://doi.org/10.36673/AJRPSB.2021.v09.i03.A14

CYTOKINE STORM IN COVID-19 PATIENT; WHAT WE KNOW

Tapas Mishra*[1], Y. Uniyal[1], Shiba S. Morris[2]

[1*]Department of Pharmacy, Kukreja Institute of Pharmaceutical Sciences, Jhajra, Dehradun, Uttarakhand, India.
[2]Gyani Inder Singh Institute of Professional Studies, Dehradun, Uttarakhand, India.

ABSTRACT

The extreme acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has reminded us of the crucial position of an effective host immune reaction and the adverse impact of immune impairment. This complete ten years because the first describe cytokine storm that evolved after chimeric antigen receptor (car) T-cell remedy and almost 27 years since the term become first used inside the literature to describe the engraftment syndrome of acute graft as opposed to-host sickness after allogeneic hematopoietic stem-cellular transplantation. The time period "cytokine launch syndrome" changed into used to describe a comparable syndrome after infusion of muromonab-CD3 (OKT3). Cytokine hurricane and cytokine release syndrome is lifestyles-threatening systemic inflammatory syndromes regarding elevated tiers of circulating cytokines and immune-cellular hyper activation that may be prompted by diverse cures, pathogens, cancers, autoimmune conditions, and monogenic issues.

KEYWORDS

COVID-19, Cytokine storm, Immunological mechanisms, Autoimmunity, Neuroimmunology, Immunotherapies, Guidelines and Critical care.

Author for Correspondence:

Tapas Mishra,
Department of Pharmacy,
Kukreja Institute of Pharmaceutical Sciences,
Jhajra, Dehradun, Uttarakhand, India.

Email: shibamorris14@gmail.com

INTRODUCTION

Earlier cytokine storm become referred as an influenza-like syndrome that happened after systemic infections which include sepsis and after immunotherapies including Coley's pollution[1-5]. A number of other problems had been defined as reasons of cytokine Strome and targeted with immune-directed treatment options, inclusive of sepsis, number one and secondary Hemophagocytic Lympho Histiocytosis (HLH), autoinflammatory problems, and coronavirus sickness 2019 (COVID-19).

In this review, we advise an Immunopathological Mechanisms, scientific considerations, and therapeutic techniques of cytokine hurricane in COVID-19 affected person Cytokine Strome is an acute hyperinflammatory response that may be accountable for crucial illness in lots of conditions including viral infections, most cancers, sepsis, and multi-organ failure. The phenomenon has been implicated in seriously ill patients inflamed withSARS-CoV-2, the novel coronavirus implicated in COVID-19. Significantly ill COVID-19 sufferers experiencing cytokine storm are believed to have a worse diagnosis and improved fatality rate. In SARS-CoV-2 infected sufferers, cytokine storm seems crucial to the pathogenesis of numerous intense manifestations of COVID-19: Acute breathing misery syndrome, thromboembolic sicknesses which include acute ischemic strokes because of huge vessel occlusion and myocardial infarction, encephalitis, acute kidney injury, and vasculitis (Kawasaki-like syndrome in kids and renal vasculitis in person). Expertise the pathogenesis of cytokine storm will help unravel not only risk factors for the situation However additionally healing techniques to modulate the immune response and supply advanced consequences in COVID-19 sufferers at high chance for extreme sickness.

No single definition of cytokine storm or the cytokine release syndrome is widely regularly occurring, and there's war of words approximately how these disorders fluctuate from the right inflammatory response. The coronavirus ailment 2019 (COVID-19) pandemic has triggered a public fitness crisis with profound long-term socioeconomic fallout. COVID-19 consequences from contamination with the extreme acute respiration syndrome coronavirus 2 (SARS-CoV-2) virus[6]. Even though the significant majority of sufferers enjoy moderate to moderate symptoms, the disease remains fatal in a significant share of these infected[7-8]. Plenty of the critical infection associated with SARS-CoV-2 infection is assumed to be the result of a hyperinflammatory procedure referred to as hypercytokinemia or a "cytokine storm"[9]. A complete expertise of the immunopathogenesis, of cytokine storm in COVID-19 patients has the potential to manual destiny strategies to improve early analysis and enforce healing techniques to mitigate cytokine typhoon-related morbidity and mortality risks[9,10]. This article discusses the implications of hypercytokinemia for COVID-19 patients, which include the chance elements for cytokine typhoon, ability healing strategies, and medical issues, with special emphasis on sufferers with most cancers, autoimmune illnesses, and people present process immunosuppressive remedies[10].

PATHOPHYSIOLOGY

Observations from the first cohort of forty one COVID-19 patients in Wuhan, which led to the invention of the radical SARS- CoV-2 virus, found out a cytokine seasonedfile just like that of secondary Hemophagocytic Lympho Histiocytosis (sHLH), a hyperinflammatory circumstance induced by way of viral infection[7]. patients who were admitted to intensive care unit (ICU) had higher ranges of granulocyte-macrophage colony-stimulating issue (GM-CSF), interferon gamma-precipitated protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis element alpha (TNFα) in comparison to individuals who were now not admitted to ICU (2). Observations from some other one hundred fifty sufferers in Wuhan found out that folks who died of COVID-19 headaches had higher serum ranges of C-reactive protein (CRP), interleukin (IL)-6 and ferritin, suggesting an underlying hyperinflammatory technique. A aggregate of those markers might also therefore be used as prognostic markers to determine COVID-19 severity.

Another study showed that patients suffering COVID-19- associated cardiac harm with the multiplied levels of troponin T (TnT) additionally proven significantly better CRP and procalcitonin degrees (up to 3–four times more) and skilled improved morbidity and mortality[7]. Patients who die from extreme COVID-19 disorder revel in

endothelial mobile infection and an endotheliitis a□ecting many organs[11,12]. The SARS-CoV-2 S protein binds to angiotensin converting enzyme 2 (ACE2) to go into host cells. Most COVID-19 patients present with respiratory signs and symptoms because ACE2 receptors are expressed in vascular endothelial cells of the lower respiratory tract[13]. In extreme COVID-19 instances, hypercytokinemia within the lungs results in di□use alveolar harm, hyaline membrane formation, thrombus formation[14], fibrin exudates, and fibrotic recovery. These pathologic changes result in acute lung injury and show up clinically as acute respiration misery syndrome (ARDS)[15]. Forty percent of COVID-19 patients revel in proteinuria and haematuria, suggesting kidneys contamination and damage[15]. COVID-19-associated kidney damage occurs due to the fact ACE2 receptors are observed within the kidney within the brush border of proximal tubular cells[16]. Even though the kidneys of COVID-19 patients examined post-mortem reveal SARS-CoV 2 antigens in the proximal tubules, the position of cytokine storm in inflicting kidney injury isn't yet clear[17].

ACE2 receptors are also present in cardiac tissue and in the gastrointestinal tract, arguably explaining the cardiac and gastrointestinal medical manifestations in some COVID-19 patients. Available statistics suggests that those with underlying cardiovascular disorder, high blood pressure, severe dyslipidaemia, obesity, and diabetes are at high threat for excessive COVID-19 disease[18], while other data suggests that SARS-CoV-2 infects the coronary heart, ensuing in myocarditis and myocardial infarctions[10,11,19-21]. Sufferers with underlying cardiovascular disease are at expanded threat of cytokine storm[8,22] and negative effects. COVID-19 patients with underlying cardiovascular sickness are also at higher chance of myocardial injury, as well as each atherosclerosis-associated and thromboembolic events which include stroke, plaque instability, vasculitis, and myocardial infarction[11,19,23]. COVID-19 has also been presumably linked to principal anxious system (CNS) signs and symptoms and conditions such as acute necrotizing encephalitis, myalgia, and headache among others even though the pathogenesis is uncertain[24-29]. As a result of the lower ACE2 expression degrees inside the CNS tissues, it has been hypothesized that the SARS-CoV-2 in keeping with se can generate little inflammation[30]. Latest autopsy studies found scarce evidence of inflammation[30-34]. Whether the switch of SARS-CoV-2 to CNS tissues potentiate or exacerbate cytokine hurricane is a subject of ongoing debate[32,33]. Immunosenescence and Cytokine typhoon elderly patients, mainly older males, with comorbidities, demonstrate elevated susceptibility to negative diagnosis or multiplied hazard of intense condition or maybe fatality from COVID-19[35]. Ageing is associated with a decline in immune feature or "immunosenescence"[36-40]. With age, the immune system can present with a sequence of adjustments, characterized via immunosenescence markers[38-40]. A decrease in the generation of CD3+T cells, an inversion of the CD4 to CD8 (CD4/CD8) T cells ratio due to the lack of CD8+T cells[39] (accelerated CD4/CD8 ratio), an increase in regulatory T cells (Treg) and a decrease in B lymphocytes[38]. It's far postulated that COVID-19 brought about cytokine strom can be contributing to the negative results in elderly patients due to immunosenescence. T lymphocytes can be probably inflamed with the aid of the virus[41]. Lowering their wide variety due to their apoptosis. Itis currently now not known whether or not the infection of the lymphocytes themselves potentiate cytokine strom. In a current look at using immunomodulatory healing approach, intravenous transplantation of mesenchymal stem cells (MSCs) changed into e□ective, in particular in seriously severe instances, in a chain of seven patients with COVID-19 pneumonia. Immunomodulatory treatments targeting cytokine hurricane show capability for such strategies in improving effects and decreasing mortality due to COVID-19 in aged sufferers.

Future studies are required to further evaluate the e□cacy of immunomodulatory therapies in preventing cytokine storm induced severe illness in

COVID-19 patients in general, and elderly patients in particular[41].

Pathophysiological mechanisms associated with COVID-19 induced cytokine storms are shown in Figure No.1.

LUNG PATHOLOGY OF COVID-19

Pathological alterations in patients with COVID-19 include pulmonary edema, diffuse alveolar harm with the formation of hyaline membranes, the presence of reactive type II pneumocyte hyperplasia, proteinaceous aggregates, fibrinous exudates, monocytes and macrophages within alveolar areas and anti-inflammatory infiltration of interstitial mononuclear cells[42-45]. Electron microscopy has discovered the presence of SARS-CoV-2 virus particles in bronchial and alveolar type II epithelial cells, but no longer in different tissues[43,44]. Therefore, although a polymerase chain response take a look at may be poor from blood or throat swabs, SARS-CoV-2 viral inclusions may be detected in the lungs. Immunohistochemical staining indicated that CD68+ macrophages, CD20+B cells, and CD8+T cells infiltrated the alveolar cavity and alveoli[43]. The ranges of CD8+T cells may be slightly better than that of CD4+T cells within the alveolar septa[46]. Those pathological features are very just like the ones of SARS-CoV and MERS-CoV infections[47,48]. Indicating that powerful remedies for SARS and MERS can be suitable for COVID-19. Excessive neighbourhood release of cytokines is considered to be the determinant of pathological alterations and the clinical manifestation of ARDS[49]. Average, the primary pathological manifestations inside the lung tissue are viral cytopathic-like modifications, infiltration of and anti inflammatory cells, and the presence of viral debris. Therefore, severe lung injury in sufferers with COVID-19 is taken into consideration because the end result of each direct viral infection and immune over activation.

MECHANISMS OF THE CYTOKINE STORM IN COVID-19

Cellular entry of SARS-CoV-2 relies upon on the binding of S proteins masking the floor of the virion to the mobile ACE2 receptor and on S protein priming by TMPRSS2, a number membrane serine protease[50]. After getting into respiration epithelial cells, SARS-CoV-2 provokes an immune response with and anti inflammatory cytokine production accompanied through a weak interferon (IFN) response. The proand anti inflammatory immune responses of pathogenic Th1 cells and intermediate CD14+CD16+monocytes are mediated through membrane-bound immune receptors and downstream signaling pathways. That is observed through the infiltration of macrophages and neutrophils into the lung tissue, which leads to a cytokine strom[51].

SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete proand anti-inflammatory cytokines, which includes granulocyte-macrophage colony-stimulating aspect (GM-CSF) and interleukin-6 (IL-6). GM-CSF in addition turns on CD14+CD16+ and anti inflammatory monocytes to provide massive portions of IL-6, tumor necrosis component-α (TNF-α), and different cytokines[52]. Membrane-certain immune receptors (eg, Fc and Toll-like receptors) can also make contributions to an imbalanced and anti inflammatory reaction, and vulnerable IFN-γ induction can be an important amplifier of cytokine production[53]. Neutrophil extracellular traps, the extracellular nets launched by means of neutrophils, may contribute to cytokine release[36]. The cytokine storm in COVID-19 is characterized by a excessive expression of IL-6 and TNF-α. Hirano and et.al proposed a capability mechanism of the cytokine storm because of the angiotensin 2 (AngII) pathway. SARS-CoV-2 activates nuclear issue-κB (NF-κB) via pattern-popularity receptors. It occupies ACE2 on the cellular floor, ensuing in a discount in ACE2 expression, followed through an growth in Ang II. Similarly to activating NF-κB, the Ang II-angiotensin receptor type 1 axis also can induce TNF-α and the soluble form of IL-6Ra (sIL-6Ra)

through disintegrin and metalloprotease 17 (ADAM17)[54]. IL-6 binds to sIL-6R through gp130 to shape the IL-6-sIL-6R complicated, that could activate sign transducer and activator of transcription 3 (STAT3) in nonimmune cells. each NF-κB and STAT3 are capable of activating the IL-6 amplifier to result in various proandanti inflammatory cytokines and chemokines, consisting of vascular endothelial boom issue, monocyte chemo attractant protein 1 (MCP-1), IL-eight, and IL-6.39 IL-6 now not most effective binds to sIL-6R to behave in cis-signaling but can also bind to the membrane-certain IL-6 receptor (mIL-6R) thru gp130 to behave in trans-signaling. The latter can result in pleiotropic consequences on obtained and innate immune cells, ensuing in cytokine storms[55,56]. Collectively, the impaired received immune responses and uncontrolled and anti-inflammatory innate responses to SARS-CoV-2 may also cause cytokine storms[57].

THERAPIES FOR THE CYTOKINE STORM IN COVID-19

Currently, many therapies are being evaluated in clinical trials due to the lack of high-quality evidence.

Corticosteroids

Corticosteroids inhibit the host and anti-inflammatory reaction and suppress the immune reaction and pathogen clearance[58]. In a retrospective observe of 401 sufferers infected with SARS-CoV, the rational use of corticosteroids shortened clinic remains and decreased the mortality of severely sick patients without complications[59-61]. However, the results of corticosteroid use in sufferers with MERS, SARS, and influenza indicated an impaired clearance of viral RNA and headaches (eg, secondary contamination, psychosis, diabetes, and avascular necrosis)[62] A current meta-analysis of 15 research determined that corticosteroids have been related to appreciably better mortality fees in patients with COVID-19[63]. Evidence suggests a potential role for using corticosteroids in patients with extreme COVID-19, caution should be exercised given the possibilities of viral rebound and adverse events.

Hydroxy Chloro Quine and chloroquine

Given their *in vitro* antiviral effects and anti-inflammatory properties, chloroquine (CQ) and its analog Hydroxyl Chloro Quine (HCQ) are considered to be ability treatments for COVID-19. Considering the excessive facet outcomes of CQ, HCQ can be a better therapeutic option. CQ and HCQ are capable of lessen CD154 expression in T cells[52] and suppress the release of IL-6 and TNF[64]. A test of the pharmacological activities of CQ and HCQ in SARS-CoV-2-inflamed Vero cells discovered that low doses of HCQ might mitigate cytokine typhoon in sufferers with intense COVID-19[65]. A small French trial showed great reductions in viral load and the length of viral contamination for COVID-19 sufferers who received 600mg/day HCQ for 10 days, and those consequences could be more advantageous via cotreatment with azithromycin[66]. Meta-evaluation of clinical trials indicated no clinical advantages of HCQ remedy in sufferers with COVID-19[67]. In reality, HCQ would possibly actually do more damage than proper given its side consequences, which include retinopathy, cardiomyopathy, neuromyopathy, and myopathy[68]. A few clinical trials have counseled that taking high doses of HCQ or CQ may reason arrhythmia[69]. The function and dangers of HCQ and CQ in the remedy of COVID-19 nevertheless need greater statistics to in addition verify.

Tocilizumab

Tocilizumab (TCZ), an IL-6 receptor (IL-6R) antagonist, can inhibit cytokine storms via blocking off the IL-6 sign transduction pathway[70]. Presently, a small-sample clinical trial in China has located TCZ to be effective in critically ill patients with COVID-19[71]. Found that out of 21 sufferers with severe COVID-19, 90% recovered after some days of remedy with TCZ. A retrospective case-manipulate observe of COVID-19 patients with ARDS discovered that TCZ may enhance survival consequences[72]. The dangers associated with TCZ (eg, excessive infections, thrombocytopenia, neutropenia, and liver harm) ought to also be stated.

Seventy three Siltuximab binds to sIL-6 and inhibits best cis- and trans-signalling. TCZ binds to both mIL-6R and sIL-6R and inhibits both cis- and trans-signalling and trans-presentation. Of note[73,74], IL-6 inhibitors aren't able to bind to IL-6 produced by means of viruses which includes HIV and human herpesvirus-8[75]. Presently, the utility of TCZ for COVID-19 remedy is under study. The three drugs noted above (corticosteroids, HCQ, and TCZ) are immunosuppressant. Owing to the overall damage to the immune system caused by autoimmune illnesses and the iatrogenic consequences of immunosuppressant, the danger of infection in patients with autoimmune sicknesses can be accelerated compared to the overall populace. currently, rheumatology societies suggest using immunosuppressive pills (besides glucocorticoids) to be suspended in sufferers with COVID-19[76-80].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have a huge variety of immune regulatory functions and can inhibit the abnormal activation of T lymphocytes and macrophages and the secretion of pro and anti inflammatory cytokines[81]. MSC remedy become observed to noticeably lessen the mortality of patients with H7N9-brought on ARDS and had no harmful facet effects[82]. A medical trial of MSC remedy discovered that MSCs were able to unexpectedly and notably improve the scientific symptoms of COVID-19 without any determined destructive results[83]. Despite the fact that the aspect consequences of MSC treatment are not often suggested, the safety and effectiveness of this treatment require further research.

Other therapies

Anakinra, an IL-1 receptor antagonist that blocks the activity of proinflammatory cytokines IL-1α and IL-1β, has been mentioned to improve the breathing function and increase the survival charge of sufferers with COVID-19[84]. IL-1 receptor antagonists boom the threat of bacterial infections, however that is extremely rare for anakinra[85] Janus kinase (JAK) inhibitors can inhibit and anti-inflammatory cytokines and reduce the ability of viruses to contaminate cells[74]. A small nonrandomized have a look at stated that patients handled with JAK inhibitors exhibited advanced scientific signs and respiration parameters[86]. JAK inhibitors can also inhibit IFN-α production, which facilitates us to combat viruses[87,88]. Intravenous immunoglobulin (IVIG) can exert numerous immunomodulatory consequences by means of blocking off Fc receptors, which are related to the severity of the and anti inflammatory state[89]. IVIG has been reportedly used to treat sufferers with COVID-19. Given its uncertain effectiveness and the chance of excessive lung injury and thrombosis[90] IVIG treatment calls for further investigation. Furthermore, convalescent plasma remedy containing coronavirus-specific antibodies from recovered sufferers may be without delay used to achieve synthetic passive immunity. This method has tested promising effects inside the remedy of SARS and influenza[91-93].

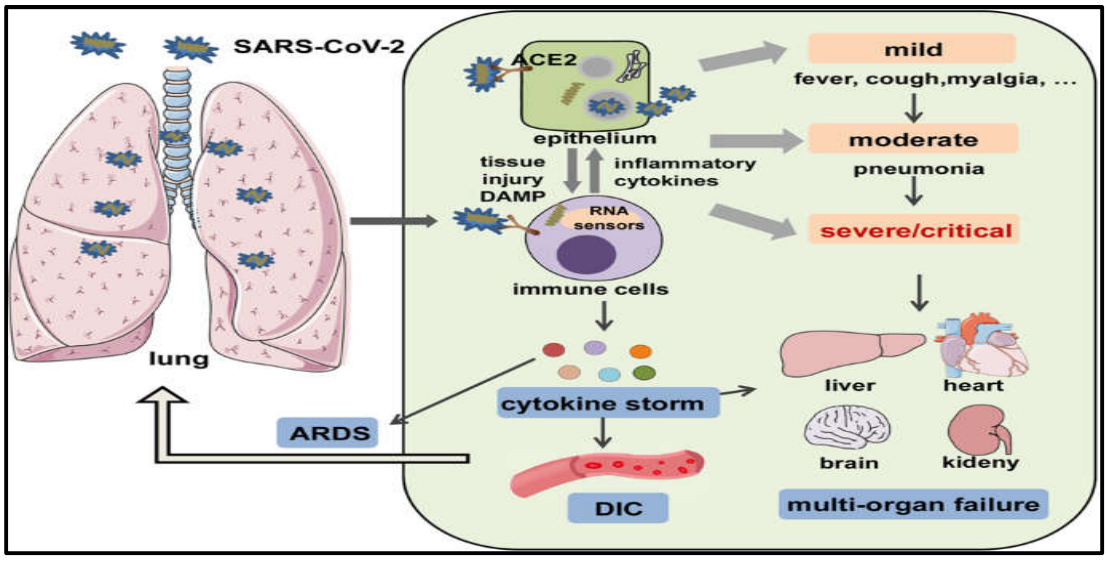

Figure No.1: Mechanisms of SARS-CoV-2 associated cytokine storm and associated damages

CONCLUSION

The cytokine strom leads to deleterious scientific manifestations or even acute mortality in critically unwell sufferers with COVD-19. Impaired received immune responses and out of control and anti inflammatory innate responses may be associated with the mechanism of the cytokine hurricane in COVID-19. Early manage of the cytokine hurricane via treatments, such as immunomodulators and cytokine antagonists, is vital to enhance the survival price of sufferers with COVID-19. Despite the fact that many research articles are published every month, most people of the prevailing literature about COVID-19 comes from descriptive works. In addition high-quality evidence could be necessary to understand and deal with the cytokine strom of COVID-19.

ACKNOWLEDGMENT

The authors wish to express their sincere gratitude to Department of Pharmacy, Kukreja Institute of Pharmaceutical Sciences, Jhajra, Dehradun, Uttarakhand, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Morgan R A, Yang J C, Kitano M, Dudley M E, Rosenberg S A. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2, *Mol Ther,* 18(4), 2010, 843-851.
2. Ferrara J L, Abhyankar S, Gilliland D G. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1, *Transplant Proc,* 25(1 Pt2), 1993, 1216-1217.
3. Coley W B. The treatment of malignant tumors by repeated inoculations of erysipelas: With a report of ten original cases, *Am J Med Sci,* 105(5), 1893, 487-511.
4. Pechous R D, Sivaraman V, Price P A, Goldman W E. Early host cell targets of Yersinia pestis during primary pneumonic plague, *PLoS Pathog,* 9(10), 2013, e1003679.
5. Mehta P, McAuley D, Brown M, Sanchez E, Tattersall R, Manson J. COVID-19: consider cytokine storm syndromes and immunosuppression, *Lancet,* 395(10229), 2020, 1033-1034.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet,* 395(10223), 2020, 497-506.

7. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China, *Intensive Care Med,* 46(5), 2020, 846-848.
8. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), *JAMA Cardiol,* 5(7), 2020, 811-818.
9. Vaninov N. In the eye of the COVID-19 cytokine storm, *Nat Rev Immunol,* 20(5), 2020, 277.
10. Weaver L K, Behrens E M. Weathering the storm: improvingtherapeutic interventions for cytokine storm syndromes by targetingdisease pathogenesis, *Curr Treatm Opt Rheumatol,* 3(1), 2017, 33-48.
11. Katsiki N, Banach M, Mikhailidis D P. Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic, *Arch Med Sci,* 16(3), 2020, 485-489.
12. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel A S, *et al*. Endothelial cell infection and endotheliitis in COVID-19, *Lancet,* 395(10234), 2020, 1417-1418.
13. Guo Y R, Cao Q D, Hong Z S, Tan Y Y, Chen S D, Jin H J, *et al*. Theorigin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, *Mil Med Res,* 7(1), 2020, 11.
14. Dolhnikoff M, Duarte-Neto A N, De Almeida Monteiro R A, Da Silva L F F, De Oliveira E P, Saldiva P H N, *et al*. Pathological evidence of pulmonarythrombotic phenomena in severe COVID-19, *J Thromb Haemost,* 18(6), 2020, 1517-1519.
15. Liu Q, Zhou Y H, Yang Z Q. The cytokine storm of severe influenza anddevelopment of immunomodulatory therapy, *Cell Mol Immunol,* 13(1), 2016, 3-10.
16. Rabb H. Kidney diseases in the time of COVID-19: Major challenges to patient care, *J Clin Invest,* 130(6), 2020, 2749-2751.
17. Perico L, Benigni A, Remuzzi G. Should COVID-19 concern nephrologists? Why and to what extent? The emerging impasse of angiotensin blockade, *Nephron,* 144(5), 2020, 213-221.
18. Bhaskar S, Rastogi A, Chattu V K, Adisesh A, Thomas P, Alvarado N, *et al*. Key strategies for clinical management and improvement ofhealthcare services for cardiovascular disease and diabetes patientsin the coronavirus (COVID-19) settings: Recommendations from the REPROGRAM Consortium, *Front Cardiovasc Med,* 7, 2020, 112.
19. Banach M, Penson P E, Fras Z, Vrablik M, Pella D, Reiner Z, *et al*. Brief recommendations on the management of adult patients with familial hypercholesterolemia during the COVID-19 pandemic, *Pharmacol Res,* 158, 2020, 104891.
20. Reiner Z, Hatamipour M, Banach M, Pirro M, Al-Rasadi K, Jamialahmadi T, *et al*. Statins and the COVID-19 main protease: In silico evidence on direct interaction, *Arch Med Sci,* 16(3), 2020, 490-496.
21. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: A cause of raised troponin and ECG changes, *Lancet,* 395(10235), 2020, 1516.
22. Madjid M, Safavi-Naeini P, Solomon S D, Vardeny O. Potential effects ofcoronaviruses on the cardiovascular system: A review, *JAMA Cardiol,* 5(7), 2020, 831-840.
23. Banach M, Serban C, Sahebkar A, Mikhailidis D P, Ursoniu S, Ray K K, *et al*. Impact of statin therapy on coronary plaque composition: A systematic review and meta-analysis of virtual histology intravascular ultrasound studies, *BMC Med,* 13(1), 2015, 229.
24. Robinson C P, Busl K M. Neurologic manifestations of severe respiratory viral

contagions, *Crit Care Explor,* 2(4), 2020, e0107.
25. Nath A. Neurologic complications of coronavirus infections, *Neurology,* 94(19), 2020, 809-810.
26. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, *et al*. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2, *Int J Infect Dis,* 94, 2020, 55-58.
27. Li Y C, Bai W Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients, *J Med Virol,* 92(6), 2020, 552-555.
28. Bhaskar S, Sharma D, Walker A H, McDonald M, Huasen B, Haridas A, *et al*. Acute neurological care in the COVID-19 era: the pandemic health systemREsilience PROGRAM (REPROGRAM) consortium pathway, *Front Neurol,* 11, 2020, 579.
29. Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu V K, Thomas P, *et al*. Chronic neurology in COVID-19 era: Clinical considerations and recommendations from the REPROGRAM Consortium, *Front Neurol,* 11, 2020, 664.
30. Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley M B, and Albrecht R, *et al*. Pathophysiology of SARS-CoV-2: Targeting of endothelial cells renders acomplex disease with thrombotic microangiopathy and aberrant immuneresponse, The Mount Sinai COVID-19 autopsy experience, *Med Rxiv,* 2020.
31. Solomon IH, Normandin E, Bhattacharyya S, Mukerji S S, Keller K, Ali A S, *et al*. Neuropathological features of COVID-19, *N Engl J Med,* 383(10), 2020, 989-992.
32. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon R E, Reidy J, Lednicky J, *et al*. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), *J Med Virol,* 92(7), 2020, 699-702.
33. Gomez-Pinedo U, Matias-Guiu J, Sanclemente-Alaman I, Moreno-Jimenez L, Montero-Escribano P, Matias-Guiu J A. Is the brain a reservoir organ for SARS-CoV2? *J Med Virol,* 92(11), 2020, 2354-2355.
34. Von Weyhern C H, Kaufmann I, Neff F, Kremer M. Early evidence ofpronounced brain involvement in fatal COVID-19 outcomes, *Lancet,* 395(10241), 2020, e109.
35. Wang L, He W, Yu X, Hu D, Bao M, Liu H, *et al*. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-weekfollow-up, *J Infect,* 80(6), 2020, 639-645.
36. Aw D, Silva A B, Palmer D B. Immunosenescence: Emerging challenges for an ageing population, *Immunology,* 120(4), 2007, 435-446.
37. Del Giudice G, Goronzy J J, Grubeck-Loebenstein B, Lambert P H, Mrkvan T, Stoddard J J, *et al*. Fighting against a protean enemy: Immunosenescence, vaccines, and healthy aging, *NPJ Aging Mech Dis,* 4, 2017, 1-8.
38. Li M, Yao D, Zeng X, Kasakovski D, Zhang Y, Chen S, *et al*. Age relatedhuman T cell subset evolution and senescence, *Immun Ageing,* 16, 2019, 24.
39. Weng N-p, A kbar A N, Goronzy J. CD28 T cells: Their role in the age-associated decline of immune function, *Trends Immunol,* 30(7), 2009, 306-312.
40. Bektas A, Schurman S H, Sen R, Ferrucci L. Human T cell immunosenescence and inflammation in aging, *J Leukoc Biol,* 102(4), 2017, 977-988.
41. Wong P, Pamer E G. CD8 T cell responses to infectious pathogens, *Annu Rev Immunol,* 21(1), 2003, 29-70.
42. Xu Z, Shi L, Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome, *Lancet Respir Med,* 8(4), 2020, 420-422.
43. Yao X H, He Z C, Li T Y, *et al*. Pathological evidence for residual SARS-CoV-2 in

pulmonary tissues of a ready-for-discharge patient, *Cell Res,* 30(6), 2020, 541-543.
44. Li H, Liu L, Zhang D, *et al*. SARS-CoV-2 and viral sepsis: Observations and hypotheses, *Lancet,* 395(10235), 2020, 1517-1520.
45. Zhang H, Zhou P, Wei Y, *et al*. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19, *Ann Intern Med,* 172(9), 2020, 629-632.
46. Azkur AK, Akdis M, Azkur D, *et al*. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19, *Allergy,* 75(7), 2020, 1564-1581.
47. Ding Y, Wang H, Shen H, *et al*. The clinical pathology of severe acute respiratory syndrome (SARS): A report from China, *J Pathol,* 200(3), 2003, 282-289.
48. Ng D L, Al Hosani F, Keating M K, *et al*. Clinicopathologic, immune histochemical, and ultrastructural findings of a fatal case of Middle East respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014, *Am J Pathol,* 186(3), 2016, 652-658.
49. Parsons P E, Eisner M D, Thompson B T, *et al*. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury, *Crit Care Med,* 33(1), 2005, 1-6.
50. Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, *Cell,* 181(2), 2020, 271-280.
51. Hussman J P. Cellular and molecular pathways of COVID-19 and potential points of therapeutic intervention, *Front Pharmacol,* 11, 2020, 1169.
52. Haiming W, Xiaoling X, Yonggang Z, *et al*. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus, *Bio RXiv,* 2020, 1-10.
53. Zuo Y, Yalavarthi S, Shi H, *et al*. Neutrophil extracellular traps in COVID-19, *JCI Insight,* 5(11), 2020, e138999.
54. Hirano T, Murakami M. COVID-19: A new virus, but a familiar receptor and cytokine release syndrome, *Immunity,* 52(5), 2020, 731-733.
55. Eguchi S, Kawai T, Scalia R, Rizzo V. Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology, *Hypertension,* 71(5), 2018, 804-810.
56. Murakami M, Kamimura D, Hirano T. Pleiotropy and specificity: Insights from the interleukin 6 family of cytokines, *Immunity,* 50(4), 2019, 812-831.
57. Moore J B, June C H. Cytokine release syndrome in severe COVID-19, *Science,* 368(6490), 2020, 473-474.
58. Chen R C, Tang X P, Tan S Y, *et al*. Treatment of severe acute respiratory syndrome with glucosteroids: The Guangzhou experience, *Chest,* 129(6), 2006, 1441-1452.
59. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia, *Lancet,* 395(10225), 2020, 683-684.
60. NIH COVID-19 Treatment Guidelines, https://www.covid19treatmentguidelines.nih.gov, 2020.
61. Russell C D, Millar J E, Baillie J K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury, *Lancet,* 395(10223), 2020, 473-475.
62. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: A systematic review and meta-analysis, *The Journal of Infection,* 81(1), 2020, E13-E20.
63. Wu S F, Chang C B, Hsu J M, *et al*. Hydroxychloroquine inhibits CD154 expression in CD4 T lymphocytes of systemic lupus erythematosus through NFAT, but not STAT5, signalling, *Arthritis Res Ther,* 19(1), 2017, 183.

64. Savarino A, Boelaert J R, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases? *Lancet Infect Dis,* 3(11), 2003, 722-727.
65. Yao X, Ye F, Zhang M, *et al*. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *Clin Infect Dis,* 71(15), 2020, 732-739.
66. Gautret P, Lagier J-C, Parola P, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, *Int J Antimicrob Agents,* 56(1), 2020, 105949.
67. Shamshirian A, Hessami A, Heydari K, *et al*. The Role of Hydroxychloroquine in the Age of COVID-19: A periodic systematic review and meta-analysis, *Med Rxiv,* 2020, 1-25.
68. Al-Bari M A. Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases, *J Antimicrob Chemother,* 70(6), 2015, 1608-1621.
69. Borba M G S, de Almeida Val F, Sampaio V S, *et al*. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (Cloro Covid-19 study), *Med Rxiv,* 2020, 1-30.
70. Lane J C E, Weaver J, Kostka K, *et al*. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: A multinational, network cohort and self-controlled case series study, *Med Rxiv,* 2020, 1-29.
71. Zhang C, Wu Z, Li J-W, Zhao H, Wang G Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality, *Int J Antimicrob Agents,* 55(5), 2020, 105954.
72. Chinese Clinical Trail Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia, 2020.
73. Xu X, Han M, Li T, *et al*. Effective treatment of severe COVID-19 patients with tocilizumab, *Proc Natl Acad Sci USA,* 117(20), 2020, 10970-10975.
74. Wadud N, Ahmed N, Mannu Shergil M, *et al*. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration, *Med Rxiv,* 2020, 1-7.
75. Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia, *Clin Drug Invest,* 40(6), 2020, 511-518.
76. Arnaldez F I, O'Day S J, Drake C G, *et al*. The Society for Immunotherapy of Cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response, *J Immunother Cancer,* 8(1), 2020, e000930.
77. EULAR guidance for patients during COVID-19 outbreak, https://www.eular.org/eular_guidance_for_patients_covid19_outbreak.cfm, 2020.
78. BSR guidance for patients during COVID-19 outbreak, *Rheumatol update-members,* https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/clinical-guide-rheumatology-patients-v2-08-april-2020.pdf, 2020.
79. ACR guidance for patients during COVID-19 outbreak, 2020. https://www.rheumatology.org/announcements, 2020.
80. Australian Rheumatology Association guidance for patients during COVID-19 outbreak, https://arthritisaustralia.com.au/advice-

regarding-coronavirus-covid-19-from-the-australian-rheumatology-association/, 2020.
81. Uccelli A, De Rosbo N K. The immunomodulatory function of mesenchymal stem cells: Mode of action and pathways, *Ann NY Acad Sci,* 1351(1), 2015, 114-126.
82. Chen J, Hu C, Chen L, *et al*. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment, *Engineering (Beijing),* 6(10), 2020, 1153-1161.
83. Leng Z, Zhu R, Hou W, *et al*. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, *Aging Dis,* 11(2), 2020, 216-228.
84. Cavalli G, De Luca G, Campochiaro C, *et al*. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: A retrospective cohort study, *Lancet Rheumatol,* 2(6), 2020, 325-334.
85. Arabi Y M, Shalhoub S, Mandourah Y, *et al*. Ribavirin and interferon therapy for critically Ill patients with Middle East respiratory syndrome: A multicenter observational study, *Clin Infect Dis,* 70(9), 2020, 1837-1844.
86. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: a pilot study on safety and clinical impact, *J Infect,* 81(2), 2020, 318-356.
87. Richardson P, Griffin I, Tucker C, *et al*. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease, *Lancet,* 395(10223), 2020, e30-e31.
88. Liu Q, Zhou Y H, Yang Z Q. The cytokine storm of severe influenza and development of immunomodulatory therapy, *Cell Mol Immunol,* 13(1), 2016, 3-10.
89. Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study, *Lancet,* 395(10223), 2020, 507-513.
90. Alijotas-Reig J, Esteve-Valverde E, Belizna C, *et al*. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review, *Autoimmun Rev,* 19(7), 2020, 102569.
91. Mair-Jenkins J, Saavedra-Campos M, Baillie J K, *et al*. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis, *J Infect Dis,* 211(1), 2015, 80-90.
92. Hung I F, To K K, Lee C K, *et al*. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection, Clin Infect Dis, 52(4), 2011, 447-456.
93. Valk SJ, Piechotta V, Chai K L, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review, *Cochrane Database Syst Rev,* 5(5), 2020, D013600.

Please cite this article in press as: Tapas Mishra *et al*. Cytokine storm in COVID-19 patient; what we know, *Asian Journal of Research in Pharmaceutical Sciences and Biotechnology*, 9(3), 2021, 119-130.