Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Special Issue Article Open Access

Mechanisms and Effectiveness of the Immunotherapy in Patients Infected with Covid-19

Allana Bandeira Carrilho, Patricia Bandeira Carrilho, Guilherme Dienstmann, Matheus Leite Ramos de Souza, Sarah Cristina dos Santos, Luzia Aparecida Venturi, Martina Dognini Antunes, Jaisa Helena Vieira, Polliane Maria Cavalcante-Araújo and Luiz Arthur Calheiros Leite*

Department of Clinical Research, Federal University of State, Rio de Janeiro, Brazil

Abstract

The Inflammation and cytokines are directly associated to the progress of COVID-19 and its severity, due to the cytokines storm and immunological pulmonary injury and systemic damage. The objective of this study was to investigate the mechanisms and effectiveness of the immunotherapy in patients infected with COVID-19. When infected, the patient develops an inflammatory chain that results in a large quantity of pro-inflammatory cytokines, the cytokines storm, leading to the fast progress of the disease. The hyperinflammation status and inflammatory biomarkers are essential tools to this disease prognostic. Therefore, the immune suppression and anti-inflammatory drugs are eligible medicaments for the therapy of cytokines storm. In this way, the immunomodulators with blockage of interleukin 6 appears as possible medicaments to inhibit in a specific way the hyperinflammation status.

Keywords: Immunomodulators; COVID-19; Cytokines

Introduction

Detected for the first time the city of Wuhan, province of Hubei in China in December of 2019, the new disease of Coronavirus 2019 (COVID-19), is a clinical syndrome caused by the etiological agent SARS-Cov-2, that was discovered after the appearance of four cases of unexplainable fever and pneumonia, through genetic isolation of the virus [1,2]. The virus quickly spread between 47 countries with 82,294 cases and further pandemical status declared by World Health Organization (WHO). The major risk groups are elderly people, patients with cardiac disease, diabetes, hypertension, pneumopathy and immunosuppressed patients [1].

The SARS-Cov-2 in an RNA virus, member of Coronaviridae family of order Nidovirales, which causes clinical manifestations in a broad spectrum, in general results in fever, cough e dyspnea. The patients with comorbidities evolve with interstitial pneumonia and fast development of acute respiratory insufficiency, septic shock, Disseminated Intravascular Coagulation (DIC), liver dysfunction and renal, being highly lethal at this stage of the disease [3,4].

When infected, viral particles enters in the pneumocytes trough Angiotensin Converting Enzyme II (ACE2) receptors, being recognized by the alveolar macrophages and dendritic cells, and develop a cellular immune mediated by T CD4 cells, activating plasma cells that results in an immune disfunction and a cytokines storm, which takes to tissue damage [2,3,5].

The cytokines are associated to the severity of COVID-19, in virtue of the increase of interleukin (IL-2, IL-6 IL-7), stimulating factors, interferon and inflammatory proteins. Hence, the lethality of the disease can be directly associated to hyperinflammation, occasioned by the virus, but this relation between the immune response to the virus and the severely of the disease stays uncertain [6-10]. In this way, the objective of this research is to investigate the mechanisms and effectiveness of the immunotherapy in patients infected with COVID-19.

The objective of this study was to investigate the mechanisms and effectiveness of the immunotherapy in patients infected with COVID-19.

Physiopathology of COVID 19

The transmission occurs by direct contact and droplets spread in the ambience, trough cough or sneezes of an infected individual. Recent studies report the presence of the virus in feces of infected person, therefore there are possibilities of fecal-oral transmission. Until the present time, there are no evidences that vertical transmission happens, because, all the contaminated expectant mothers are being submitted to cesarean section and the cases of reinfection are rare [10,11]. It was estimated that 44% of transmissions occurs before the emergence of symptoms, such as fever and cough in the majority part of cases. However, there are no other symptoms related, like dyspnea, sore throat, fatigue, myalgia and vomit [12,13].

The virus has tropism for cells with ACE receptors, widely expressed in alveolar epithelial cells (around 83%), as well as nasal mucosa, bronchi, lungs, heart, esophagus, kidneys, stomach, liver, urinary bladder and ileus. Therefore, this consolidates the fact that the pulmonary tissue, as the pneumocytes, are more affected, resulting in respiratory disorders [11,14].

The immunological response starts to the invasion of the virus through the airways, via nasopharynx e oropharynx, reaching the lungs. Then, the viral particle gets in touch with alveolar macrophages, dendritic cells and epithelial cells that activates the inflammatory chain and releases a large amount of proinflammatory cytokines, the cytokines storm. Afterwards the antigen presenting cells signalize to the T CD4 lymphocytes, with more release of cytokines and increase of the pulmonary inflammation process, well as activate the T CD8 cytotoxic cells, which attacks the SARS-Cov-2. After the beginning of the humoral response via Th2 cell, the plasmocytes are stimulated to produce anti-SARS-Cov-2 antibodies that attach to the virus and destroys them. However, with the cytokines storm and the hyperinflammation status pneumopathies can happen, that progresses to SARS, septic status and multiple organ failure [15].

The incubation period of COVID-19 occurs on an interval between

***Corresponding author:** Luiz Arthur Calheiros Leite, Department of Clinical Research, Federal University of State, Rio de Janeiro Brazil, E-mail: lahemato@gmail.com

Received: July 01, 2020; **Accepted date:** July 15, 2020; **Published date:** July 21, 2020

Citation: Carrilho AB, Carrilho PB, Dienstmann G, De Souza MLR, Dos Santos SC, et al. (2020) Mechanisms and Effectiveness of the Immunotherapy in Patients Infected with Covid-19. J Infect Dis Ther S2: 002.

Copyright: © 2020 Carrilho AB, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

2 and 14 days [16]. In immunosuppressed patients, the emergence of symptoms can be longer than that interval, reaching up to 20 days the incubation period. In this patients, clinical manifestations can be atypical and without respiratory symptoms [17].

The severity of the disease ranges from asymptomatic, mild, moderate, severe and critical. In severe cases, patients can develop SARS, from 8 to 12 days after the symptom's onset [18].

Epidemiology

The new virus, SARS-Cov2 emerged in China and spread around the world and the disease started to be considered a pandemic, by World Health Organization (WHO) in March 2020 [16].

At the beginning of July 2020, there were more than 10 million of infected cases around the world with 507 thousand deaths. The epicenter of the disease has moved from China, and the United States held the position with over 2,7 million cases and 128,692 thousand deaths, followed by Brazil with 1,4 million cases and 59,656 thousand deaths, 617 thousand cases in Russian and 9,320 thousand deaths, and more than 180 countries showed infection for SARS-Cov2 [19]. The mortality rate around the world has a variation between 3,4 up to 10%, being higher, mainly, in European countries that took more time to take containment measures and for having an elderly population [13].

The mortality rate increases according to the raise of the age groups, making the elderly people, the individuals with higher death risk. The patients, who do not have pre-existing diseases, present a lower rate than those who have; however, a lot of the infected individuals are oligosymptomatic or asymptomatic, being carriers, transmitting and disseminating the disease in a large scale [20].

Diagnostic Features

To the accomplishment of the diagnostic, additionally to the evaluation of the clinical manifestations observed during the physical examination and anamnesis of the suspect patient, medical exams must be done to discard other viral or respiratory diseases. In laboratorial exams, it is observed in the hemogram a leukocytosis and a neutrophilia related to the inflammatory process or bacterial co-infections, lymphopenia by error at the immune response and viral infection with possible destruction of T lymphocytes, thrombocytopenia by consumption coagulopathy linked to higher levels of D dimer [21].

With the disease's progression there is a gradual increase on lactate dehydrogenase, C reactive protein and ferritin levels due to the cytokines storm, raise of transaminases with decrease of albumin due to liver damage. In cases that progress to sepsis with Disseminated Intravascular Coagulation (DIC), there is an increase of D-dimer and extended time of prothrombin by development of microthrombus. Morphological anomalies were observed in patients with COVID-19 such as dysplastic myelocytes and promyelocytes, pseudo-pelger like by defect in the myelopoiesis, and presence of circulating reactive lymphocytes [12,21-24].

Another exam that shows indicative signals of infection by COVID-19 is chest area Computerized Tomography (CT), that in axial cuts demonstrates bilateral multifocal ground glass like opacities, over two pulmonary lobes and with predominance in the lower lobes, that intensifies according to the increase of the disease extent. Although, the CT should not be done to diagnostic intentions, but yes to follow-up the stages of the disease [12,25]. Invasive exams, like bronchoscopy or pulmonary biopsy, should be used on a last resource and after discussion about its necessity due to high dissemination viral infection control measures.

To confirmation of the disease quick testing should be done with blood samples by immunochromatographic method, which detects positive IgM antibodies and negative IgG, indicating a recent immune response from 7 days or less, from the beginning of symptoms, with benefits for its practicality and quickness to detect the result in a few minutes. The confirmation can be done by the RT-PCR serology, trough the collection of material with swab in nasopharynx, to detection of virus and the viral load [11].

Immune Response and Immunosuppression

Covid-19 induces a pro-inflammatory response with an exacerbated release of cytokines, such as IL-6, which plays a central role, as a mediator of lung inflammation and fever. At high levels, interleukin 6 inhibits the initiation of the immune response through T cells and dendritic cells, resulting in lung tissue damage, which is a clinical manifestation widely, observed in patients with SARS, as well as high concentrations of IL- 6 in the blood [26]. In addition, IL-6 is a strong inducer of C-reactive protein [27].

The hyperinflammation of the cytokine storm can facilitate viral replication and damage the microvascular barrier of the pulmonary alveoli, causing edema and damaging the lung parenchyma. These manifests itself with the unexpected worsening of symptoms, such as dyspnea, noticed in the evolution from moderate to severe state, consequently the increase of cytokines becomes a severity marker of the disease [28].

In a study conducted with 171 patients, an increase in IL-6 levels was observed with the worsening of the disease and these values were higher in patients who died. Therefore, high levels of this interleukin are probably responsible for lethal complications in covid-19 and can be considered a risk factor for mortality [29].

Several studies, in which the use of IL-6 blockers in patients with Covid-19 was evaluated, claim that this treatment, with immunosuppressant, is effective and brings benefits to critically ill patients who are being assisted in the Intensive Care Unit (ICU), since the use of these antagonists potentially reduces the harmful immune response caused by SARS-coV-2 [30-32]. On the other hand, the immune compromise of patients undergoing immunosuppressive therapy may result in an increased prevalence of infections by other pathogenic microorganisms [33].

According to studies, immunocompromised patients are more vulnerable to the infection, which in most cases can result in fatalities [26]. The patient's vulnerability was evidenced by the high mortality risk during the period of Middle East Respiratory Syndrome (MeRS) outbreak, in 2015, additionally to the risk of infection to these exposed patients [34]. However, a new study done by the Korean Society of Infectious Diseases and Korea Centers for Disease Control and Prevention analyzed the mortality of 54 patients with COVID-19, in which there were 8 immunocompromised patients in being seven patients with cancer and one receptor of kidney transplant) and this represented 14,8% of deaths in general [35].

The virus that triggered the outbreak in the Middle East is similar to the current pandemic, in addition to belonging to the same family. However, there is a disparity in mortality levels, since in the SARS virus, lethality is presented in a similar way in groups of immunocompromised and non-immunocompromised.

The SARS-Cov-2, as well as the Human Immunodeficiency Virus

(HIV), uses the humoral immune response to infect the target cell from the host, where few antibodies are capable of increase its efficiency of replication, weakens the immunological system and reduces body's capability of battling infections [36,37]. In relation to COVID-19 and HIV, a research which evaluated 5 patients with immunocompromise by HIV, where four of them were suppressed virologically, developed issues, infections on superior respiratory tract and viral pneumonia, but none progressed to death [38].

According to Ogimi et al. witch evaluated 1237 patients and compared the clinical conditions characteristic from COVID-19 between immunocompromised children and non-immunocompromised, it was observed the respiratory co-pathogens were detected more commonly on the non-immunocompromised group, as well as infections in the superior respiratory tract and the presence of feverish disease [39]. Nonetheless, the infections of the inferior respiratory tract did not differ between the groups.

In accordance with another study, a patient with cancer and immunocompromised had her chemotherapy suspended after manifestation of fever and being diagnosed of pneumonia by SARS CoV-2 infection, presented significant leukopenia 1300 mm3, neutropenia 600/mm3 e lymphopenia, 600/mm3, indicating an immunosuppression state. She did not present severe complications and had a benign course of the disease, while a second patient which she was compared, non-immunocompromised, had severe complications and a slower recovery [8].

Severe stage to critical stage evolution can develop the known as cytokines storm, which has a hyperinflammation due to the increase of immune response, leading to a quick progression of the disease. This evolution is usually milder in patients already made use of immunosuppressors before the infection by COVID-19, since immunomodulators reduce IL-6 levels and stabilize respiratory conditions, not having necessity to intubation. So, the treatment for cytokines storm is fundamental to the recovery of severe patients [40,41].

Patients with COVID-19 and depletion of B cells and that did not develop severe complications, could be related to the persistence of this cells inside secondary lymphoid organs. As an consequence, the immune response is reduced, as well as cytokines, due the lack of peripheral B cells, performing a positive role to the patient and resulting in a good prognostic [42].

Therapeutic Evidences

All severe patients with COVID-19 should be tracked about hyperinflammation trough laboratorial exams, to identify who could reduce the mortality rate with immunosuppression. The use of glucocorticoids in the treatment of cytokines storm, can delay the virus elimination and cause complications, therefore new therapies should be used. The therapeutic options include steroids, intravenous immunoglobulin, selective block of cytokines and inhibition of Janus kinase 2 (JAK-2) [6].

The IL-6, as well as other cytokines produced in high levels during the response to the viral infection in severe patients, become a prognostic marker of severity of pulmonary complications by COVID-19, since deregulates the inflammatory responses [26] (Tables 1-3).

Parameter	Clinical mechanisms
↓ Lymphocytes	Decrease of the immune response against the virus
↓ Platelets	Platelets consumption
↑ Troponin	Cardiac compromise/organ failure
↑ D Dimer	Consumption coagulopathy
↑ Alanine aminotransferase (AST) and Aspartate aminotransferase (ALT)	Liver compromise/organ failure
↓ Albumin ↑ ferritin	Renal compromise/hyperinflammation/ organ failure
↑ C Reactive Protein (CRP)	Hyperinflammation e Cytokines storm
↑ Interleukin 6 (IL-6)	Hyperinflammation e Cytokines storm

Table 1: Prognostic Biomarkers in COVID-19 Patients.

- Oncological Patients
- HIV carriers
- Autoimmune diseases carriers
- Patients that make use of corticosteroids
- Transplanted patients

Table 2: Immunocompromised groups that used immunosuppressors.

DRUG	MECHANISM OF ACTION	POTENTIAL USAGE IN COVID-19
Tacrolimus(TAC)	Immunosuppressor inhibitor of calcineurin enzyme	Reduces the activity of immune system, as well as the release of cytokines, improving the radiological findings.
Tocilizumab	Monoclonal antibody IL-6 receptor antagonist, that blocks the transduction of interleukin 6 signal.	Reduces the fever, CPR levels, and abnormalities in computerized tomography. However, can ease the inflammation and induce fibrosis.
Adalimumab	Monoclonal antibody, anti-TNF, TNF receptor antagonist, one of the main mediators of inflammatory response and production of cytokines	Reduce pulmonary abnormalities and reduces the risk of septic shock.
Leronlimab	Humanized monoclonal antibody antagonist of CCR5 receptor on T CD4 lymphocytes.	Changes macrophages migration and the production of cytokines. Additionally, stops the viral replication.
Anakinra	Antagonist of IL-1 receptor, interleukin also released on the cytokines storm.	It works on macrophages activation syndrome of septic patients.
Intravenous Immunoglobulin (IVIG)	Competitive blocker of the Fc receptor (FcR), which prevents its activation on the viral connection and viral endocytosis.	It works reducing the production of inflammatory cytokines and avoids severe pulmonary injuries, due the reduction of viral replication.
Baricitinib e Ruxolitinib	JAK inhibitors immunomodulators, blocks the virus entry in the cells.	Limits systemic inflammatory responses, reducing cytotoxic T lymphocytes and increases Treg.

Table 3: Immunosuppressors and inflammatory inhibitors and therapeutic usage in COVID-19.

It's worth to mention, that, in accordance with some studies, immunosuppression can be a worsening factor to coronavirus, because it contributes to the increase of susceptibility to infection, and can be related to atypical clinical presentations, with severe complications [43,44]. Immunosuppression harms the induction of antiviral response and also can stimulate the development of secondary bacterial infections and get worse even more the prognostic of the disease. Therefore, immunosuppressors should be associated to efficient antiviral therapy,

to avoid an uncontrolled infection and worse the disease. The benefits should be carefully evaluated against the potential of compromising antimicrobial immunity [45,46].

Conclusion

COVID-19 is an infectious disease induced by a virus that causes imbalance of the immune system and inflammatory cytokines storm. Patients immunosuppressed by autoimmune, oncological, transplanted diseases, using corticosteroids, as well as HIV patients treated when infected with SARS-Cov-2, usually do not have severe forms of the disease, possibly due to the decreased immune response. Another possibility would be that protease inhibitors may act by preventing viral proliferation of the coronavirus.

Considering that the status of hyperinflammation and inflammatory biomarkers are essential tools for the prognosis of this disease, immunosuppression and anti-inflammatory drugs are eligible drugs for the treatment of the cytokine storm. Thus, immunomodulators with interleukin 6 block appear as possible drugs to specifically inhibit the status of hyperinflammation. However, further studies are needed to assess the effectiveness of immunotherapy in patients infected with COVID-19.

Acknowledgements

We would like to express our sincere condolences to the patients and their families who suffered with the SARS-Cov-2 outbreak. We also appreciate to the Health professionals that keep working and have trying to control the pandemic on behalf of the population.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Yan XU, Hongsheng LI, Ke HU, Mengzhao WA (2020) Clinical management of lung cancer patients during the outbreak of 2019 novel coronavirus disease (COVID-19). Zhongguo Fei Ai Za Zhi 23(3):136-141.
2. Prompetchara E, Ketloy C, Palaga T (2020) Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 38:1-9.
3. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A (2020) Middle East respiratory syndrome. Lancet 395:1063-1077.
4. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G (2020) Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. Cell Stress 4:66.
5. Lin L, Lu L, Cao W, Li T (2020) Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 9:727-732.
6. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, et al. (2020) COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 395:1033.
7. Yi Y, Lagniton PN, Ye S, Li E, Xu RH (2020) COVID-19: What has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci 16:1753.
8. Spezzani V, Piunno A, Iselin HU (2020) Benign COVID-19 in an immunocompromised cancer patient-the case of a married couple. Swiss Med Wkly 150:w20246.
9. The LO (2020) COVID-19: Global consequences for oncology. Lancet Oncol 21:467.
10. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 26:102433.
11. Jin Y, Yang H, Ji W, Wu W, Chen S, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Virus 12:372.
12. Siordia Jr JA (2020) Epidemiology and clinical features of COVID-19: A review of current literature. J Clin Virol 10:104357.
13. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, et al. (2020) Clinical features of covid-19. BMJ 369:m1470.
14. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, et al. (2020) COVID-19, cytokines and immunosuppression: What can we learn from severe acute respiratory syndrome?. Clin Exp Rheumatol 38:337-342.
15. Li X, Geng M, Peng Y, Meng L, Lu S (2020) Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 10:102-108.
16. Sahu KK, Mishra AK, Lal A (2020) COVID-2019: Update on epidemiology, disease spread and management. Monaldi Arch Chest Dis 90.
17. Romanelli A, Mascolo S (2020) Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: A therapeutical hypothesis. Am J Transplant 20:1947-1948.
18. Tenda ED, Asaf MM (2020) Diagnosing COVID-19: Did We Miss Anything?. Acta Med Indones 52:1-4.
19. Who. Situation report – 102. Coronavirus disease 2019 (COVID-19). 01 May 2020. Disponível em:
20. Sun K, Chen J, Viboud C (2020) Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: A population-level observational study. Lancet Digit Health 2:e201-e208.
21. Lippi G, Plebani M (2020) Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 58:1131-1134.
22. Frater JL, Zini G, d'Onofrio G, Rogers HJ (2020) COVID-19 and the clinical hematology laboratory. Int J Lab Hematol 1:11-18.
23. Zini G, Bellesi S, Ramundo F, d'Onofrio G (2020) Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol 95:870-872.
24. Ye Q, Wang B, Mao J (2020) Cytokine storm in COVID-19 and treatment. J Infect 80:607-613.
25. Lima CM (2020) Informações sobre o novo coronavírus (COVID-19). Radiol Bras 53:V-I.
26. Russell B, Moss C, George G, Santaolalla A, Cope A, et al. (2020) Associations between immune-suppressive and stimulating drugs and novel COVID-19: A systematic review of current evidence. Ecancermedicalscience 14: 1022.
27. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ (2020) 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 55:105954.
28. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, et al. (2020) Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev 4:102567.
29. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 395:1054-1062.
30. Liu B, Li M, Zhou Z, Guan X, Xiang Y (2020) Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)?. J Autoimmun 111:102452.
31. Tufan A, GÜLER AA, Matucci-Cerinic M (2020) COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 50:620-632.
32. Zhao M (2020) Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents 55:105982.
33. Diamanti AP, Rosado MM, Pioli C, Sesti G, Laganà B (2020) Cytokine Release Syndrome in COVID-19 Patients, A New Scenario for an Old Concern: The Fragile Balance between Infections and Autoimmunity. Int J Mol Sci 21:3330.
34. Jazieh AR, Al Hadab A, Al Olayan A, AlHejazi A, Al Safi F, et al. (2020) Managing Oncology Services During a Major Coronavirus Outbreak: Lessons From the Saudi Arabia Experience. J Glob Oncol 6:518-524.
35. Park SH, Lee MS, Kim SR, Kwak YG, Kwon K, et al. (2020) Analysis on 54 mortality cases of coronavirus disease 2019 in the Republic of Korea from January 19 to March 10, 2020. J Korean Med Sci 35:e132.
36. Wang SF, Tseng SP, Yen CH, Yang JY, Tsao CH, et al. (2014) Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun 451:208-214.

37. Moni MA, Liò P (2014) Network-based analysis of comorbidities risk during an infection: SARS and HIV case studies. BMC Bioinformatics 15:333.

38. Blanco JL, Ambrosioni J, Garcia F, Martínez E, Soriano A, et al. (2020) COVID-19 in patients with HIV: Clinical case series. Lancet HIV 7(5):e314-e316.

39. Ogimi C, Englund JA, Bradford MC, Qin X, Boeckh M, et al. (2019) Characteristics and outcomes of coronavirus infection in children: The role of viral factors and an immunocompromised state. J Pediatric Infect Dis Soc 8:21-28.

40. Gandolfini I, Delsante M, Fiaccadori E, Zaza G, Manenti L, et al. (2020) COVID-19 in Kidney Transplant Recipients. Am J Transplant 20:1941-1943.

41. Zhang S, Li L, Shen A, Chen Y, Qi Z (2020) Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. Clin Drug Investig 40:511-518.

42. Novi G, Mikulska M, Briano F, Toscanini F, Tazza F, et al. (2020) COVID-19 in a MS patient treated with ocrelizumab: Does immunosuppression have a protective role?. Mult Scler Relat Disord 42:102120.

43. Guery B, Poissy J, El Mansouf L, Séjourné C, Ettahar N, et al. (2013) Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: A report of nosocomial transmission. Lancet 381:2265-2272.

44. Dholaria B, Savani BN (2020) How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? Br J Haematol 189:239.

45. Ritchie AI, Singanayagam A (2020) Immunosuppression for hyperinflammation in COVID-19: A double-edged sword? Lancet 395:1111.

46. Fishman JA, Grossi PA (2020) Novel Coronavirus-19 (COVID-19) in the immunocompromised transplant recipient: Flatteningthecurve. Am J Transplant 20:1765-1767.