Curr. Pharm. Res. **2020**, *11[1],* 4073-4088

Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Review Article

Immunity: Defense Against Sars-Cov-19

Jenu Shivaji*, Samruddhi Sitapure, Drishti Umralkar, Aishwarya Valiyaparambath, Dhanashri Raskar, Pallavi Sontakke, Ketan Bhutkar

KJ's Educational Institute's Trinity College of Pharmacy, Pune, Maharashtra, India.

Received 28 October 2020; received in revised form 02 December 2020; accepted 29 December 2020

***Corresponding author E-mail address:** *jane2001daniel@gmail.com*

ABSTRACT
SARS-CoV-19 is a very contagious disease resulting in pneumonia and lung failure, which has become the cause of death in many cases. The studies and research for vaccination is going on. Many studies and researches have pointed out the importance of strengthening our immunity, as it is the first line of defense. Researchers have pointed out the need of a strong immune system and its effect on the expulsion of viruses from our system. In case of a weak immunity, like in the case of old age and various pathological conditions, various immunotherapies and several types of vaccines, monoclonal antibody candidates, etc. can be effective and these methods can be used to prevent the entry of the virus in our system and even if it enters, decrease its effect on our system, hence decreasing cases, which would need ventilator or ICU, care, but the study on them in still in progress.

KEYWORDS
Coronavirus, Hyper-inflammation, Immunoglobulin, Monocyte, Pneumocytes, Ventilation, Immunotherapy.

1. INTRODUCTION

Acute Respiratory Disease is prompted by way of a novel coronavirus (SARS-Cov-2), previously known as 2019-nCoV, the coronavirus disease 2019 has spread at some point in China and has obtained international attention. On 30 January 2020, the World Health Organization (WHO) formally declared the COVID-19 epidemic as a major concern affecting public health internationally. The virus originated in bats and became transmitted to human beings via yet unknown middleman animals in Wuhan, Hubei Province, China in December 2019. The ailment is transmitted by using inhalation or contact with infected droplets and incubation period tiers from 2 to14 days.[1] Typical coronavirus particles are 80-140nm in diameter, with 20-40nm complicated floor projections surrounding the outer edge have been seen under electron microscopy.[2] A Novel Coronavirus became identified in the blood, respiratory specimens (or pharyngeal became, nasopharyngeal aspirate, sputum and lung biopsy) and stools of SARS patients by using various research groups. [4-6] SARS is in most cases a respiratory disorder and the highest awareness of the virus can be found inside the respiration tract. The infection at the incubation period stages from 2-6 days before the fever occurs. Most patients' fever settles inside 2 weeks and that is observed by means of decision of chest signs. [3][7] In the bulk of instances, mild signs and symptoms like fever and cough are observed however in approximately 10-20% of instances which led to pneumonia and breathing disasters required ventilation support. Along with direct contact transmission, many other risk factors are also worried like age, health troubles such as persistent pulmonary or cardiac disease situations in addition to vintage age-associated conditions and obesity. These factors also decide the mortality rate. [10-13]

For now, there are no precise treatment options or vaccines for this disease but studies are going on that are focusing on various factors like immunity. In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic [43]

The spreading of COVID-19 involves four phases as follows [42, 48]

I) Phase I (Slowing the spread): First identified with travel history, no local spread and infection would be low

II) Phase II (State-by-State Reopening): It is locally transmitted via travel history; the virus spread close contact with infected person

III) Phase III (Establish Immune Protection and Lift Physical Distancing): Infection in locally public and source is not traced; in this case, larger geographical areas should be locked down and start isolation to avoid rapid transmission of community infection.

IV) Phase IV (Rebuild Our Readiness for the Next Pandemic): This phase is the disease is going on epidemic and pandemic. The infections and a growing number of deaths with no end in sight. Large number of infections will grow and it is uncontrollable, a large number of people will be dead.

In analysis of 75,465 COVID-19 cases in China, airborne transmission was not reported [42, 44, 47] With the help of computed tomographic scans it has been observed that post surgery patients developed pneumonia related to COVID-19 and the symptoms include fever [91.2%], fatigue [73.5%] and dry cough [52.9%] and [44.1%] patients were admitted to the intensive care unit (ICU) during disease progression. [45, 46]

SARS CoV-2 has a structure containing four structural proteins envelope (E), spike (S), membrane (M) and nucleocapsid (N) as shown in Fig.1 [53,54]

The spike glycoprotein (S) is on the virion of surface medicate receptor recognition and membrane fusion spike glycoprotein comprised of the trimeric S units divided into S1 and S2 subunits. [54-57]

In the progress to the post combination compliance S1 units are discharged. Therefore S1 units contain the receptor binding domain (RBD) which directly binds to the peptidase domain (PD) of ACE2 for which membrane fusion S2 is responsible. [58]

The S protein of the SARS CoV-2 may utilize ACE2 for host infection as shown in Fig.2 [52][61-63] Spike is the main protein that interacts with host cell receptors. Spike protein has 2 units S1 and S2. In the first step spike protein is cleaved into S1 and S2 by the host cell proteases, one of which is transmembrane proteases. Studies in mice demonstrated that binding of spike protein S1 with ACE2 regulates the receptors and thereby contributes to severe injury (Refer Fig. 6). [55][59-60]

Spike glycoprotein binds to the human ACE2 receptor present in the target cell in the respiratory tract. A site is present in the protein that makes it possible for the virus to bind better than other viruses with the same origin. [58]

Once the spike protein binds with the host receptor, the viral genome of the coronavirus enters into the target cell. [52][61-63]

In the complex structure, with N-linked glycosylation at N343, the SARS-CoV-2-CTD contains 195 consecutive density-traceable residues which span T333 to P527 together. Similar to several other CTD structures reported for beta CoV, this protein also showcases two structural domains.

In SARS-CoV-2, alanine replaces threonine, and leucine replaces isoleucine. Previously it has been shown that replacing Ser284, Thr285, and Ile286 with alanine residues in SARS-CoV Mpro triggers a factor of 3.6 to improve the protease catalytic function, in accordance with a somewhat closer packing of the two domains III of the dimer against one another (refer Fig. 3). [64]

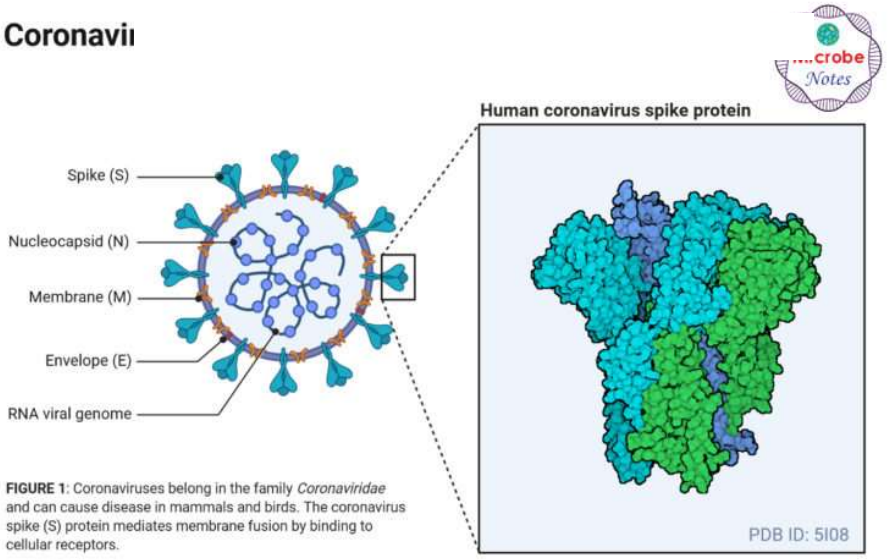


Fig. 1. Coronavirus Structure and protein Visualization [66]

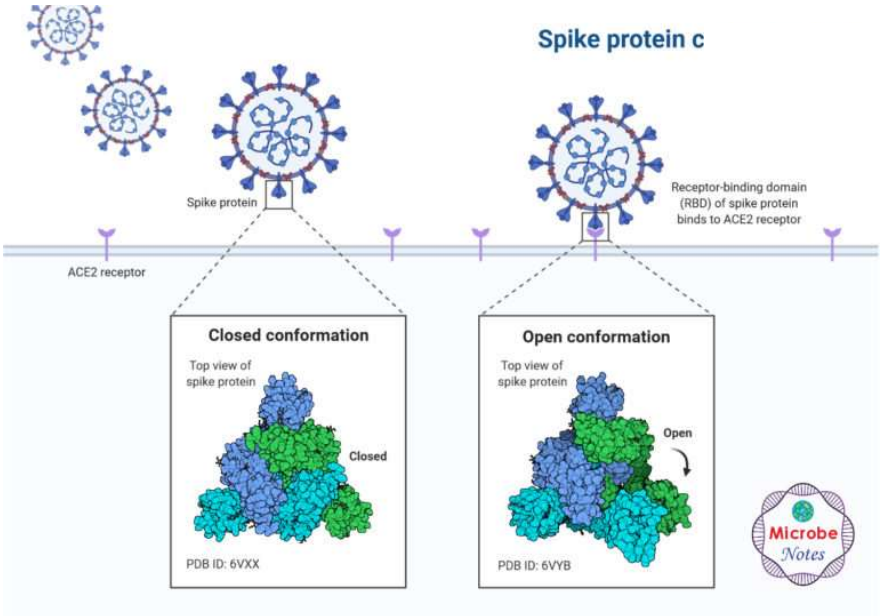


Fig. 2. Spike protein conformations [67]

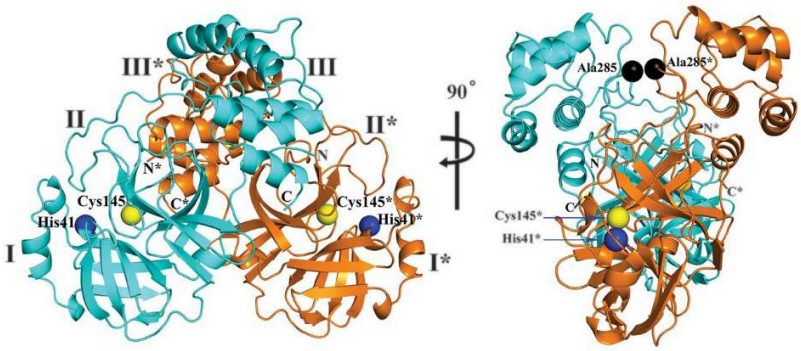


Fig. 3. Three dimensional structure of SARS-CoV-2 Mpro [65]

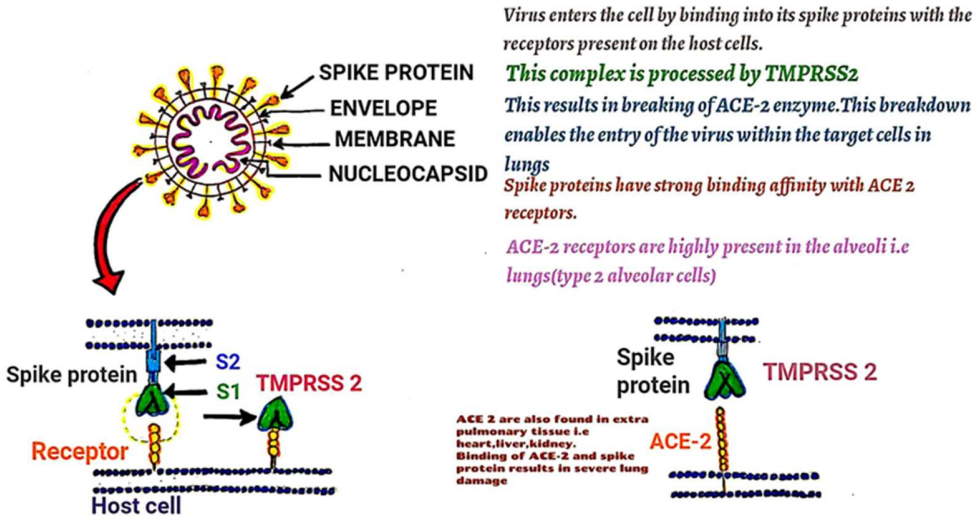


Fig. 4. Binding of TMPRSS2 and ACE 2 to spike proteins

1. Progression of The Pathogen in The Body

After the virus enters the body, the virus attacks the epithelial cells and type II pneumocytes by binding its spike proteins with the Angiotensin Converting Enzyme 2 (ACE2). This complex is then processed by the type 2 transmembrane protease TMPRSS breaking the ACE2 enzymes. The breakdown of ACE2 enzyme activates the spike proteins and enables the entry of the virus within the target cells in the lungs as shown in Fig.4 [8][20] After the entry of the virus inside the cell it releases its positive RNA single strand into the cells and through the virus polymerase reaction, it replicates its strands and multiply in number within the cell, targeting the host cell

mechanism. [26] The positive strand then enters the nucleus of the cell and proceeds to hijack the mechanism of the cell by inhibiting the phosphorylation reaction as shown in Fig.6.

Binding of SARS-CoV-S to ACE2 in reduced ACE2 expression leads to acute acid-aspiration-induced lung failure.[12] SARS-CoV-2 uses angiotensin converting enzyme II (ACE2) and transmembrane serine protease 2 (TMPRSS2) as cell entry receptors, followed by a cytokine-related syndrome, ARDS, which is induced by the hyper-activation of the transcription factor NF-κB. [8] As a result certain method must be performed to prevent their binding with each other as shown in Fig.5.

These type 2 cells highly express both ACE2 and TMPRSS 2 enzymes and receptors respectively. Therefore, it can be said that these type 2 cells are the primary entry of COVID-19 into the lungs cells. Therapeutic targets which are aiming to prevent the binding of ACE2 and the spike proteins are only for the first phase not for the latter phase because in the latter phase there is an extreme inflammation which cannot be stopped and results in an ARDS mediating death. ARDS is a lethal syndrome caused by pneumonia and sepsis due to cytokine syndrome. [33][35][36]

Even gas exchange is also affected. When immune cells attack the virus they also harm the normal alveoli cells. This results in collapsing of alveoli because of the loss of surfactant produced by the type II cells (Type II cells produce the surfactant which line the walls of alveoli and prevent the collapsing of alveoli) and less oxygen enters the body because of the lack of type I cells (Type I cells are responsible for the diffusion of oxygen through the walls of alveoli because they are thin walled). This results in the accumulation of fluid within the alveoli [30].

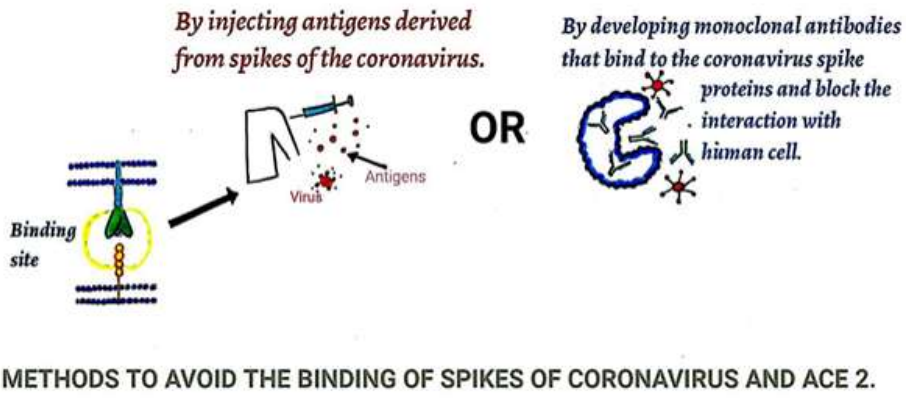


Fig. 5. Methods to avoid the binding spikes of coronavirus and ACE 2

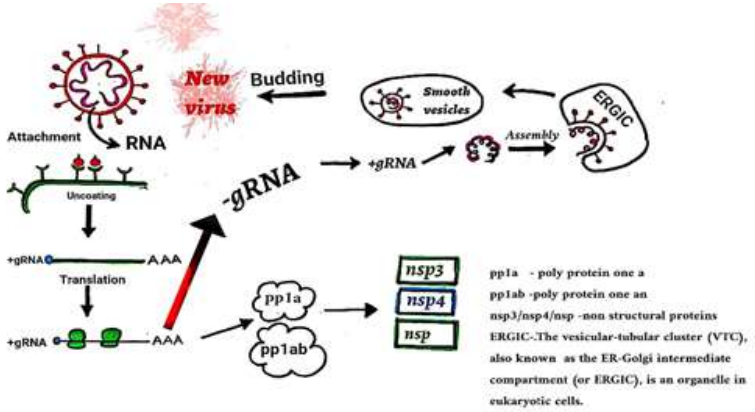


Fig. 6, Multiplication of RNA of coronavirus in host cell

2. Immune Response Observed in The Body

The body reacts spontaneously to viral invasion with a non-specific inherent immune response in which non-immune cells delay the virus' development, and can even prohibit it from causing symptoms. Once the non- specific response is activated, immediately adaptive immunity comes into effect. The function of adaptive immunity is to make antibodies and these antibodies attach to the virus and prevent its replication and further growth. Here T-cells play an important role by recognizing and eliminating virus-infected cells at cellular level and this is called cellular immunity.

The immunity responses are activated in the body through many mechanisms. First is the induction of inflammatory reaction through MyD88 and TRIF mediated pathway, which is activated by the Toll-like receptors, TLR3 and TLR4 at the entry of the virus in the body. The second mechanism is the release of inflammasomes through the IL-6 pathway, which is also responsible for the hyper inflammation observed in the SARS-CoV-19 patients [21-23]

In both scenarios, the induction of innate immune response triggers the antiviral host defence mechanism, which in turn triggers the release of danger signals like cytokines, and chemokines that contribute to the inflammation and tissue damage in the later stages.

At the same time, the natural killer cells, which are a part of innate immunity cells, are activated on the activation of the innate immunity. The Natural killer cells have the property to eliminate abnormal and stressed cells naturally in cancerous conditions. They also play an important role in the destruction of virus affected cells. But dimerization of NKG2A and CD 94 which is an inhibitory receptor that inhibits the activation of NK cells leads to the increase in the workload on the cytotoxic lymphocyte leading to their exhaustion. This is another reason for complications in SARS COVID-19 patients especially in severely affected patients. It is observed that the endothelial cells play an important role in coordinating the inflammatory sequelae via sphingosine-1-phosphate signalling by reducing cytokine responses resulting in respiratory infections. But these S1P1-specific agonists do not affect adaptive immune response and viral replication.

The studies also show that severely affected patients have high levels of neutrophil count, lymphocyte count, total Bilirubin, lactate dehydrogenase in blood. Levels of alanine aminotransferase and acetate aminotransferase are also slightly higher in severe cases, indicating severe lung and liver damages.

The following record focuses on the importance of immune response of natural killer cells as it avoids the depletion of cytotoxic lymphocytes in the initial stage of SARS CoV-19 infection. Therefore functional depletion of cytotoxic lymphocytes can be prevented by targeting NKG2A receptors. [12][31]

The inflammation produced in the nose and upper respiratory regions produces mucus and running nose which prevents the entry of viral pathogens by trapping them or expelling them out of the respiratory tract through sneezing. Inflammation is also observed in the sinuses which produces headache and generates stuffiness related with cold. [25]

The inflammation also triggers the fluid accumulation in the air sacs of alveoli, which results in pneumonia preventing oxygen from getting through affecting the blood oxygen level, causing severe breathing difficulties. [27] In the brain, the hypothalamus gets inflamed because of lack of oxygen supply, which causes fever. This fluid contains T-cells that damage many normal cells and expelling this fluid produces dry cough.

Studies also show the increase in systemic inflammatory reactions, which is observed in the SARS-CoV-19 ICU patients. This is when cytokines are produced. It also results in endothelial dysfunction reflection because of the elevated level of d- dimers and hyperactivity of T- cells in the lungs. [29]

This leads to severe immune response in the body leading to the excess production of cytokines in the blood resulting in the phenomena called cytokine storm because of which hyper inflammation is observed. Major complications can be seen in those patients who have respiratory failures due to hyperactive inflammation, which eventually leads to Adverse Respiratory Syndrome.

3. Boosting Immunity

The first line of defence is the innate immunity against attacking pathogens which enter our body. When this first line of defence is profuse then the adaptive immunity is activated. This includes T and B-lymphocytes. The adaptive immunity has immunological memory in which cell mediated part consists of cytotoxic T cells that kills the infected cells as it can specifically recognize the antigen that the body has formerly experienced thereby preventing their growth by eliminating the pathogens. [26]

This characteristic of adaptive immunity is very efficient in its process and therefore is very important for the defence mechanism of the body. In most of the CoV-19 patients, it is observed that unrestricted viral replication results in a high concentration of virus, which in turn triggers the hyperactive- inflammation and ADRS and leads to death in many cases. This is observed in patients having defects or weak immunity.

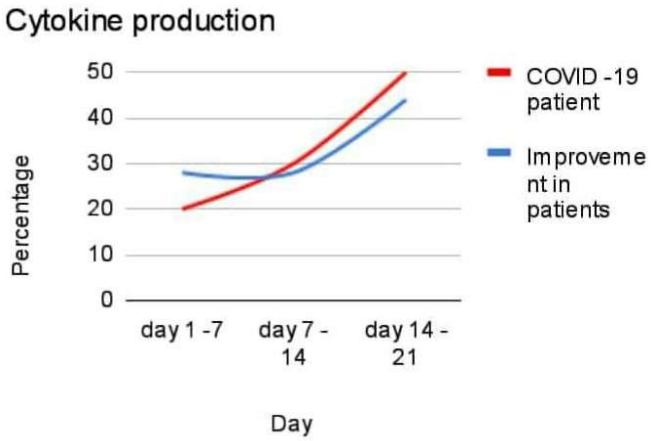
Therefore, to control the replication of the virus in the unaffected host and to minimize the effect and infection of the pathogen in the affected host, boosting our immunity through various immunotherapies has become an important stage in preventing the spreading of the infection.

In most of the cases, the symptoms appeared between 7 to 14 days. At the detection of the antigen or pathogen, the innate immunity is activated. However, since the virus multiplies at a higher rate and destroys the host mechanism, cytokine is produced. However, the amount of cytokine is so high; it not only attacks the virus- infected cells but produces hyperactive inflammation which is called CRS.

This condition is observed in the ICU admitted patients. At the time of admission in the hospital, the inflammation is not severe, but since the production of the cytokine is high and the multiplication of the virus is also more, it results in systemic inflammation with the collapsing of the lung.

As shown in the graph, the cytokine production is at its highest peak between the 14th and 21st day, the curve does not decrease.

Therefore, to prevent organ failure, the focus should be on decreasing the peak of the cytokine production from the high to intermediate level, which will at least prevent systemic inflammation thereby preventing organ failure.



Therefore this can be achieved by interrupting the hyper inflammatory loop. The activation of the IL-6 pathway is responsible for the release of the cytokine, which is responsible for the hyper- inflammation. This pathway is eventually responsible for the damage of lung tissue in many CoV-19 cases. At the same time, elevated levels of TNF-alpha and IFN-g have been consistently observed in cytokine release syndrome. Severe CRS can also lead to hypotension, pulmonary oedema and cardiac dysfunction that are commonly observed in severely ill CoV-19 patients. These provide justification for targeting the IL-6 pathway. Therefore, in this case it is preferable to use IL-6 pathway inhibitors. [25]

Various studies are going on in which the innate immunity is modified to develop the immunological memory of the adaptive immunity. This can be developed by repeated attack of

one particular pathogen or by an efficient vaccine. For this to happen durable epigenetic modification of the innate immunity cell is needed. Along with this, various metabolic processes are also taken into account as they function as co- regulatory molecules for the epigenetic enzymes. This therapy is also known as trained immunity. This therapy will boost the innate immunity and will strengthen the first line of defence, which is very important in case of a CoV-19 patient.

IVIG (Intravenous Immunoglobulin) Therapy is an alternative technique and one of the most widely used immune therapies for a large no. of autoimmune and inflammatory diseases. IVIG not only suppresses the activation of inflammatory cytokines but also subdues its secretion from the innate immune cells and blocks the inflammatory Th1 and Th17 response by exerting damaging effects on the system and enhances the Tregs. [14][15] The studies also show that variables such as dose, time of infusion and duration of therapy play a very important role and it was observed that the beneficial effects are associated with high dose and early IVIG treatment. [16]

Beneficial results can be obtained from the vaccines of passive immunotherapy. Studies on Cov-19 confirmed the presence of sero-converted antibodies, such as IgG, IgM and IgA with varying kinetics and sensitivities. Findings in the monkey SARS CoV-2 infection model confirmed that primary infection could protect the host from reinfection perhaps aided by humoral responses. Therefore, passive immunization of SARS-CoV-2 is obtained by using convalescent plasma, intravenous hyper immunoglobulin (containing high concentrations of neutralizing antibodies obtained from the pooled plasma of a larger number of recovered patients.) [17]

Small-molecule tyrosine kinase inhibitors and cytokine targeting antibodies demonstrate remarkable clinical efficacy but they are broadly immunosuppressive and not applicable to the full spectrum of autoimmune diseases. These challenges are driving efforts to develop more targeted therapies, such as adoptive transfer of Tregs, which play a major role in preserving self-tolerance, maintaining immunity homeostasis, and preventing autoimmunity. [32]

If the Treg number is affected in any person it results in part severe inflammation and lung damage which is observed in many of the CoV-19 patients. Since this therapy is expensive and requires a lot of time, therefore adoptive Tregs therapy is not feasible for CoV-19 patients who are in urgent need of treatment. However, this method can be employed by IL-2 based therapies, which can be used to expand Tregs, and Tregs- derived therapeutic molecules. [18]

Along with these therapies, several NK (Natural Killer) cell based approaches are under consideration. These NK cells can competitively inhibit SARS-CoV-2 infection of susceptible cells including alveolar epithelial cells. Although the strategy looks rational, the toxicity due to virus infected lung cells should be controlled and monitored accordingly. [19]

According to the studies done on the previous virus cases like the H1N1 and influenza cases it has been observed that the endothelial cells play an important role in coordinating the inflammatory sequelae via sphingosine-1-phosphate signalling by reducing cytokine responses resulting in respiratory infections. But these S1P1-specific agonists do not affect adaptive

immune response and viral replication in vivo, therefore can be used in the treatment of inflammatory reaction observed in CoV-19. [34]

Many other drugs, especially pathway inhibitors, are under evaluation as a treatment for SARS-CoV-2. Among which is the hydroxychloroquine that is used in the treatment of malaria. This drug is observed to prevent aggravation of the disease and viral persistence with the combination of some other drug. It increases the pH of lysosomes and hence prevents the replication and fusion of CoV-19. Other drugs include BCG (Bacillus Calmette- Guerin) vaccination used in the treatment of TB, Oral polio vaccine and corticosteroids and many other drugs are under the evaluation. [24] [25] But the most important fact is the window period between the contact of infection and the treatment. If the treatment is delayed even for a few hours, it can result in severe infection. [49]

Lastly, our diet, what we eat is also a very important factor in strengthening our immunity which includes micronutrients like vitamins A, B complex, C, D and E and folic acid, iron, riboflavin, selenium and zinc. These help to increase resistance for infection. Vitamins also preserve the antioxidant balance in our body by counteracting the influence of free radicals. They also bear the burden of ensuring immune competence. Various vitamins have various functions but are very crucial to maintain the body functioning correctly. Vitamin A tends to control intrinsic immunity and the immunity generated by cells. It also decreases the susceptibility to diseases and cancers. Deficiency of vitamin B6 can lead to impairment of the lymphocyte response, the production of antibodies, T cell function and the reduction of thymus glands. Vitamin B12 deficiency stands in the way of WBC maturation and multiplication. Vitamin C was studied as the potential nutrients for antivirals and anticancer drugs. Vitamin D receptors are located on the T cell and B- cell surface. They perform a very significant function in autoimmune disorders as the immunosuppressant. Zinc is an essential component for immune cell proliferation. Selenium helps regulate the functions of the antioxidants and redox functions. Therefore, a balanced proportion of all the vitamins and minerals should be present in our diet. [50] [51]

4. CONCLUSION

In our body, immunity is the primary protection against the pathogens that enter our body. Without it our body would be under the attack of pathogens constantly. Even, in this case, when the Cov-19 enters and replicates its viral RNA in the host cell, the first immune response is the release of cytokines. But in many cases the macrophages get activated more than needed and it results in a cytokine storm which results in hyper inflammation and systemic inflammation. Hyperactive inflammation is the primary reason for the ADRs and various other pathological symptoms, related to Cov-19. So to overcome this, inhibitors can be used but inhibiting this process can lead to inhibition in the immune response, which will not be a good option in patients having severe symptoms. Therefore, to overcome this problem, researchers are suggesting various immunotherapies and methods to train and strengthen both our innate as well as adaptive immunity. To prevent the entry of the virus in our system and even if it enters,

decrease its effect on our system, hence decreasing cases, which would need ventilator or ICU care.

5. ACKNOWLEDGEMENT

We wish to especially thank our Prof. Ketan Bhutkar for the support, guidance and insightful knowledge on this subject. We would also like to thank our esteemed institute Trinity College of Pharmacy, Pune for providing us with this opportunity.

REFERENCE

1. Yan-Rong Guo 1Qing-Dong Cao 2, Zhong-Si Hong 3, Yuan-Yang Tan , Shou-Deng Chen 1, Hong-Jun Jin 1, Kai-Sen Tan4, De-Yun Wang 4*and Yan Yan; The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status; uo et al. Military Medical Research (2020) 7: 1https://doi.org/10.1186/s40779-020-00240-0
2. Tanu Singhal 1; A Review of Coronavirus Disease-2019 (COVID-19); The Indian Journal of Pediatrics; https://doi.org/10.1007/s12098-020-03263-6
3. Lee, N. et al. (2003) A major outbreak of severe acute respiratory syndrome in Hong Kong. New Engl. J. Med. 348, 1986–1994
4. Książek, T.G. et al. (2003) A novel coronavirus associated with severe acute respiratory syndrome. New Engl. J. Med. 348, 1953–1966
5. Drosten, C. et al. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl. J. Med. 348, 1967–1976
6. Peiris, J.S.M. et al. (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361, 1319–1325
7. Peiris, J.S.M. et al. (2003) Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361, 1767–1772A
8. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., et al. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11, 875-879.
9. A Dynamic Immune Response Shapes COVID-19 Progression; authors Eugenia Ziying Ong,1,2 Yvonne Fu Zi Chan,3 Wan Ying Leong,1,2 Natalie Mei Ying Lee,3 Shirin Kalimuddin,2,3 Salahudeen Mohamed Haja Mohideen,4 Kian Sing Chan,5 Anthony Tanoto Tan,2 Antonio Bertoletti,2 Eng Eong Ooi,1,2,3,* and Jenny Guek Hong Low1,2,3,6,*; doi.org/10.1016/j.chom.2020.03.021
10. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497-506.
11. Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-h., Ou, C.-q., He, J.-x., Liu, L., Shan, H., Lei, C.-l., Hui, D.S.C., et al. (2020). Clinical Characteristics of Coronavirus Disease 2019 in

China. New Engl. J. Med. published online February 28, 2020. https://doi.org/10.1056/NEJMoa2002032

12. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270-273.

13. 4. Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., Cereda, D., Coluccello, A., Foti, G., Fumagalli, R., et al. (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. Published online April 6, 2020. https://doi.org/10.1001/jama.2020.5 94

14. Schwab, I. and Nimmerjahn, F. (2013). Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat. Rev. Immunol. 13, 176-189

15. Galeotti, C., Kaveri, S.V., and Bayry, J. (2017). IVIG-mediated effector functions in autoimmune and inflammatory diseases. Int. Immunol. 29, 491-498

16. Xie, Y., Cao, S., Li, Q., Chen, E., Dong, H., Zhang, W., Yang, L., Fu, S., and Wang, R. (2020). Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J. Infect. Published online April 10, 2020. https://doi.org/10.1016/j.jinf.2020.0 044

17. Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J., Lv, Q., Liu, J., Yu, P., Xu, Y., et al. (2020). Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv. Published online March 14, 2020. https://doi.org/10.1101/2020.03.13.990226

18. Webster, K.E., Walters, S., Kohler, R.E., Mrkvan, T., Boyman, O., Surh, C.D., Grey, S.T., and Sprent, J. (2009). In vivo expansion of T reg cells with IL-2–mAb complexes: induction of resistance to EAE and long-term acceptance of islet allografts without immunosuppression. J. Exp.

19. S.R., Kaveri, S.V, Sakuntabhai, A., Gilardin, L., Bayry, J., Adjunct immunotherapies for the management of severely ill COVID-19 patients, Cell Reports Medicine (2020), doi: https://doi.org/10.1016/j.xcrm.2020.100016.

20. Glowacka, I., Bertram, S., Müller, M.A., Allen, P., Soilleux, E., Pfefferle, S., Steffen, I., Tsegaye, T.S., He, Y., Gnirss, K., et al. (2011). Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J. Virol. 85, 4122–4134.

21. Sheahan, T., Morrison, T.E., Funkhouser, W., Uematsu, S., Akira, S., Baric, R.S., and Heise, M.T. (2008). MyD88 Is Required for Protection from Lethal Infection with a Mouse-Adapted SARS-CoV. PLoS Pathog. 4, e1000240.

22. Shi, C.S., Nabar, N.R., Huang, N.N., and Kehrl, J.H. (2019). SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov. 5, 101.

23. Ong, E.Z., Yvonne Fu Zi Chan, Wan Ying Leong, Natalie Mei Ying Lee, Shirin Kalimuddin, Salahudeen Mohamed, Haja Mohideen, Kian Sing Chan, Anthony Tanoto

Tan, Antonio Bertoletti, et al. (2020). A dynamic immune response shapes COVID-19 progression. Cell Host Microbe

24. Goodridge, H.S., Ahmed, S.S., Curtis, N., Kollmann, T.R., Levy, O., Netea, M.G., Pollard,
A.J., Van Crevel, R., and Wilson, C.B. (2016). Harnessing the beneficial heterologous effects of vaccination. Nat. Rev. Immunol. 16, 392–400.

25. Netea, M.G., Giamarellos-Bourboulis, E.J., Domínguez-Andrés, J., Curtis, N., van Crevel, R., van de Veerdonk, F.L., Bonten, M., Trained immunity: a tool for reducing susceptibility and severity of SARS-CoV-2 infection, Cell (2020), doi: https://doi.org/10.1016/j.cell.2020.04.042.

26. https://en.wikipedia.org/wiki/Coronavirus

27. https://www.nationaljewish.org/patients-visitors/patient-info/important-updates/coronavirus-information-and resources/ health-tips/ about- covid-19/covid-19-and-your-lungs

28. Regulatory T Cells (TREG) and Their Roles in Immune System With Respect to Immunopathological Disorders; Katerina Kondělková et al. Acta Medica (Hradec Kralove). 2010.

29. Grifoni, A., Weiskopf, D., Ramirez, S.I., Mateus, J., Dan, J.M., Moderbacher,C.R., Rawlings, S.A., Sutherland, A., Premkumar, L., Jadi, R.S., Marrama, D., de Silva, A.M., Frazier, A.,Carlin, A., Greenbaum, J.A., Peters, B., Krammer, F., Smith, D.M., Crotty, S., Sette, A., Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals,Cell (2020), doi: https://doi.org/10.1016/j.cell.2020.05.015.

30. https://www.visualcapitalist.com/wp-content/uploads/2020/04/covid-19-affects-the-body.html

31. Chen, N. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395, 507–513 (2020).

32. Sakaguchi, S., Yamaguchi, T., Nomura, T., and Ono, M. (2008). Regulatory T cells and immune tolerance. Cell 133, 775–787.

33. Neelapu, S.S., Tummala, S., Kebriaei, P., Wierda, W., Gutierrez, C., Locke, F.L., Komanduri, K.V., Lin, Y., Jain, N., Daver, N., et al. (2018). Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat. Rev. Clin. Oncol. 15, 47–62.

34. Teijaro, J.R., Walsh, K.B., Cahalan, S., Fremgen, D.M., Roberts, E., Scott, F., Martinborough, E., Peach, R., Oldstone, M.B.A., and Rosen, H.(2011). Cell 146, this issue, 980–991.

35. de Wit, E., van Doremalen, N., Falzarano, D., and Munster, V.J. (2016). SARS and MERS: recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 14, 523–534.

36. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., et al. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS

coronavirus-induced lung injury. Nat. Med. 11, 875–879.

37. https://en.wikipedia.org/wiki/CD94/NKG2

38. Rosen, H., Gonzalez-Cabrera, P.J., Sanna, M.G., and Brown, S. (2009). Annu. Rev. Biochem. 78, 743–768.

39. https://en.wikipedia.org/wiki/Sphingosine-1-phosphate.

40. https://courses.lumenlearning.com/boundless-ap/chapter/adaptive-immunity/

41. World Health Organization. Guidance for Managing Ethical Issues in Infectious Disease Outbreaks. Available from: https://apps.who.int/iris/rest/bitstreams/1063213/retrieve.

42. WHO, Health Emergency and Disaster Risk Management Framework. 2019, WHO: Geneva.

43. WHOCoronavirusDisease(COVID-19)Dashboard https://www.who.int/news-room/q-a-detail/q-a-coronaviruses

44. Panel Catrin Sohrabia1 Zaid Al safib1 Niamh O' Neilla Mehdi Khanb Ahmed World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19), Volume 76, April 2020, Pages 71-76.

45. CatrinSohrabia,ZaidAlsafib,NiamhO'Neilla,MehdiKhanb,World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19), April 2020.

46. Syed Adeel Hassan, Fahad N. Sheikh, Somia Jamal, Jude K. Ezeh, Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment,March 19, 2020.

47. 43Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations, Scientific brief,29 March 2020

48. 44Marco Cascella; Michael Rajnik; Arturo Cuomo; Scott C. Dulebohn; Raffaela Di Napoli, Features, Evaluation and Treatment Coronavirus (COVID-19),March 20, 2020.

49. Center for Disease control and prevention, Information for Clinicians on Therapeutic Options for Patients with COVID-19 Updated April 7, 2020 , https://www.cdc.gov/coronavirus/2019-ncov /hcp/therapeutic-options.html

50. Semba RD. Vitamin A as "anti-infective" therapy, 1920-1940. J Nutr. 1999;129:783-791.

51. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr. 1999;69(6):1086-1107.

52. . P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C. -L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X. -R.Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature (2020). doi:10.1038/s41586-020-2012-7 Medline

53. 2. T. M. Gallagher, M. J. Buchmeier, Coronavirus spike proteins in viral entry and pathogenesis. Virology 279, 371–374 (2001). doi:10.1006/viro.2000.0757 Medline

54. 3. G. Simmons, P. Zmora, S. Gierer, A. Heurich, S. Pöhlmann, Proteolytic activation of the SARS-coronavirus spike protein: Cutting enzymes at the cutting edge of antiviral

research. Antiviral Res. 100, 605–614 (2013). doi:10.1016/j.antiviral.2013.09.028 Medline

55. 4. S. Belouzard, V. C. Chu, G. R. Whittaker, Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc. Natl. Acad. Sci. U.S.A. 106, 5871–5876 (2009). doi:10.1073/pnas.0809524106 Medline

56. 5. G. Simmons, J. D. Reeves, A. J. Rennekamp, S. M. Amberg, A. J. Piefer, P. Bates, Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. Proc. Natl. Acad. Sci. U.S.A. 101, 4240–4245 (2004). doi:10.1073/pnas.0306446101 Medline

57. 6. W. Song, M. Gui, X. Wang, Y. Xiang, Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLOS Pathog. 14, e1007236 (2018). doi:10.1371/journal.ppat.1007236 Medline

58. 7. F. Li, W. Li, M. Farzan, S. C. Harrison, Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science 309, 1864–1868 (2005). doi:10.1126/science.1116480 Medline

59. 8. J. K.Millet, G. R.Whittaker, Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 202, 120–134 (2015). doi:10.1016/j.virusres.2014.11.021 Medline

60. 9. G. Simmons, D. N. Gosalia, A. J. Rennekamp, J. D. Reeves, S. L. Diamond, P. Bates, Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc. Natl. Acad. Sci. U.S.A. 102, 11876–11881 (2005). doi:10.1073/pnas.0505577102 Medline

61. 10. M. Hoffmann, H. Kleine-Weber, N. Krüger, M. Müller, C. Drosten, S. Pöhlmann, The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv2020.01.31.929042 [Preprint]. 31 January 2020. https://doi.org/10.1101/2020.01.31.929042.

62. 11. W. Li, M. J. Moore, N. Vasilieva, J. Sui, S. K. Wong, M. A. Berne, M. Somasundaran, J. L. Sullivan, K. Luzuriaga, T. C. Greenough, H. Choe, M. Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426, 450–454 (2003). doi:10.1038/nature02145 Medline

63. 12. K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W.Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A.Leibbrandt, T. Wada, A. S. Slutsky, D. Liu, C. Qin, C. Jiang, J. M. Penninger, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat. Med.11, 875–879 (2005). doi:10.1038/nm1267 Medline

64. L. Lim, J. Shi, Y. Mu, J. Song, PLOS ONE 9, e101941 (2014).

65. https://www.chemistryworld.com/news/potent-coronavirus-drug-candidate-designed-using-3d-structure-of-key-viral-enzyme/4011411.article

66. https://microbenotes.com/coronavirus/

67. https://microbenotes.com/structure-and-genome-of-sars-cov-2/