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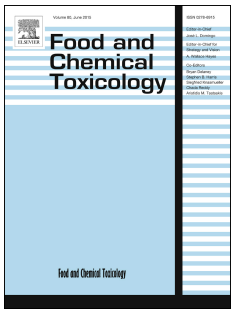

Inflammation, immunity and potential target therapy of SARS-COV-2: a total scale analysis review

Shukur Wasman Smail, Muhammad Saeed, Twana alkasalias, Zhikal Omar Khudhur, Delan Ameen Younus, Mustafa Fahmi Rajab, Wayel Habib Abdulahad, Hafiz Iftikhar Hussain, Kamal Niaz, Muhammad Safdar

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Author Contributions

All the authors have equally contributed.

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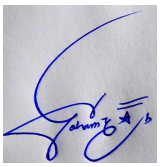

Dr. Muhammad Safdar

Inflammation, immunity and potential target therapy of SARS-COV-2: a total scale analysis review

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Abstract

Coronavirus disease-19 (COVID-19) is a complex disease that causes illness ranging from mild to severe respiratory problems. It is caused by a novel coronavirus SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2) that is an enveloped positive-sense single-stranded RNA (+ssRNA) virus belongs to coronavirus CoV family. It has a fast-spreading potential worldwide, which leads to high mortality regardless of lows death rates. Now some vaccines or a specific drug are approved but not available for every country for disease prevention and/or treatment. Therefore, it is a high demand to identify the known drugs and test them as a possible therapeutic approach. In this critical situation, one or more of these drugs may represent the only option to treat or reduce the severity of the disease, until some specific drugs or vaccines will be developed and/or approved for everyone in this pandemic. In this updated review, the available repurpose immunotherapeutic treatment strategies are highlighted, elucidating the crosstalk between the immune system and SARS-CoV-2. Despite the reasonable data availability, the effectiveness and safety of these drugs against SARS-CoV-2 needs further studies and validations aiming for a better clinical outcome.

Keywords: Coronavirus disease-19; Immunotherapeutic drugs; Repurpose; Severe Acute Respiratory Syndrome Coronavirus 2; Monoclonal antibodies; Vaccine.

1. Introduction

As of January 26, 2021, a sum of 100,346,160 confirmed cases of the COVID-19 have been revealed in 210 nations and territories around the world (1), that is due to the virus named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) originated from Wuhan, China in December 2019 (2). Depending on clinical manifestations, the COVID-19 is grouped into mild, moderate, and severe. In severe cases of COVID-19, the patients exhibit hyper inflammation and cytokine storms (CS) that drive acute lung injury (ALI), acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (3), multiple organ failure and death (2).

SARS-CoV-2 is a new strain of Coronavirus that's newly capable of infecting humans (4). It is a +ssRNA virus, even though the origin is not yet clear. The source could be from bats as it shares 96% similarity with coronaviruses (CoVs) isolated from bats RaTG13 complete genome (5). It might be transferred to humans through a missing link as an intermediate host that could be scaly ant-eater (pangolin) based on an amino acid chain in the receptor-binding domain (RBD) of CoVs discovered in pangolins or snake (6).

The SARS-CoV-2' corresponded CS is characterized by increasing level of inflammatory cytokines and chemokines (interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, interferon-γ-inducible protein (IP10), decreasing level of helper (T_h) and cytotoxic T-lymphocytes (CTLs), down-regulating the interferon (IFN)-γ expressing T_h cells (7, 8). This hyperinflammatory state produces oxidative stress that leads to damage to alveolar and endothelial cells in the lung. The damage of these cells disrupts the pulmonary barrier and vascular leakage that consequently enhances lung edema and ARDS.

Chemokines recruit the macrophage and neutrophil into the lung that causes ALI (9). COVID-19 patients with CS exhibit a high level of IL-6 (10), that have a major role in coagulation, disseminated intravascular coagulation (DIC), and multiple organ failure including heart (11).

Yet, there are some vaccine and medications for preventing or curing the disease. There is a wide variety of therapeutics that have been explored to treat COVID-19, initially suggested for other diseases and already established safety profiles and approved by the food and drug Administration (FDA). Such treatments are referred to by the World Health Organization (WHO) (12) as repurpose medications (12). Among them, the antivirals drugs such as favipiravir, umifenovir, remdesivir, lopinavir, and retonavir, the antimicrobial agents such as chloroquine and hydroxychloroquine, anthelmintics (ivermectin), antihypertensives (Losartan) (13, 14), and known immunotherapies; are currently used as a treatment option. There are many ongoing clinical trials regarding the safety and effectiveness of repurposing immunotherapeutics to mitigate the symptoms of COVID-19 (15).

The purpose of the current review is to highlight and discuss the immunotherapeutic options to treat COVID-19, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, monoclonal antibodies, IFNs, convalescent plasma, and other treatments that are known to have immune-modulatory properties. Such immunotherapeutic showed promising efficacy against other CoVs including severe acute respiratory syndrome-coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome-CoV (MERS-CoV), and other viruses that might have the potential for SARS-CoV-2 treatment and

prophylaxis. This might help scientists and pharmaceutical industries to design an appropriate immune intervention for COVID-19 therapy.

2. Methodology

For current study a bibliographic search of more than 420 peer-reviewed papers in scientific data including PubMed, Scopus, Science Magazine, EMBASE, WHO and Google Scholar about SARS-CoV-2 was done. But approximately 337 peer-reviewed papers relevant to SARS-CoV-2 were included as shown in Figure 1A. All scientific data was reviewed with key words of “SARS-COV-2 structure”, “cell tropism of SARS-CoV-2”, “clinical presentation of COVID-19”, “immune response to COVID-19”, “cytokines and immunopathogenesis of SARS-CoV-2”, “immunotherapeutic strategies”, “monoclonal antibodies for COVID-19”, and “treatment strategy COVID-19”.

3. SARS-CoV-2: structure and cell tropism

CoVs are classified under the *Coronaviridae* family within *Nidovirales* order; which comprises other families such as *Roniviridae* and *Arteriviridae*. The classification is based on the conserved genome organization and viral genomic replication mechanisms (16). CoVs possess enveloped virions and +ssRNA genomes. These viruses are capable of infecting a wide variety of animal species in addition to human beings (17). The main source of CoVs transmission is through close contact with an infected person via respiratory droplets (18). According to the type of invading virus, other diseases may be initiated e.g., neurological disease and hepatitis (19).

Based on the comparisons of the whole genome sequence of the CoVs, they can be divided into alpha-CoVs and beta-CoVs groups which may cause diseases in mammals,

including the humans (20-22). The third group gamma-CoVs; the fourth group delta-CoVs; include viruses that mainly cause diseases in birds (20, 23). There are some controversies about whether to classify SARS-CoV-2 into a new group. Despite that SARS-CoV-2 has numerous distinctive characteristics; however, the genetic variation in the viral genome is insufficient to include it into a new group. The succeeded investigations concluded that beta-CoV is the best group that fits SARS-CoV-2 (24).

CoVs have a distinct feature of the coronal structure, regarding the name corona (crown-like) that represents projections covering the envelope when examined under the electron microscope (25). These spike-shaped particles are virion of roughly spherical or polymorphism shapes within 80nm-160nm diameters (26). In general, the morphology of the virion particles of SARS-CoV-2 represents a model of CoVs shape. A lipid bilayer covers the outer margins of most virions (27). To fill the gap in the understanding of the origin of SARS-CoV-2, a team of researchers had collaborated after one month of the epidemic to establish the first genome sequence of the virus by January 10, 2020 (28). The sequenced genome was determined to be 29,811 base pairs long (29), which made SARS-CoV-2 one of the largest +ssRNA viruses identified to date. More than ten open read frames (ORFs) are presented within the SARS-CoV-2 genome, similar to that of SARS-CoV-1, both viruses have the order and organization of the same genes. Two-thirds of the SARS-CoV-1 genome is occupied by ORF1a/1b, which is the most imperative ORF and is translated into 16 nonstructural proteins (NSP 1-16). Four structural proteins (SPs); spike (S) protein, matrix (M) protein, nucleocapsid (N) protein, and envelope (E) protein are translated from other ORFs in the remaining genome (30).

The genes in the rest ORFs coded into accessory proteins that are not recognized to have any function in viral replications (31).

The fusion of the SARS-CoV-2 virus to the host surface membrane is mediated by the two functional subunits S1 and S2 of the S surface proteins (32). The S1 subunit binds to the host cellular receptor, and then the S2 subunit fuses with the cellular membrane (33). The entry point for the SARS-CoV-2 is delivered by a functional receptor metallopeptidase angiotensin converting-enzyme 2 (ACE2) (34) (35). Tissue tropism of SARS-CoV-2 is best elucidated by the ACE2 localization in most organs such as the heart, kidney, vascular endothelial, testis as well as epithelial of the small intestine and alveolar epithelial cells (36-38).

4. Clinical presentation of COVID-19

The COVID-19 is divided into three stages based on the severity of the disease (39): stage 1 is a mild stage characterized by an asymptomatic period in which the virus may or may not be measured; stage 2 is a moderate stage in which the virus is detected followed by pneumonia; stage 3 is the severe stage with high load of the virus, usually followed by severe pneumonia, ALI, ARDS and CS (4). The incubation period of the disease varies among the cases, but it is usually between 2-14 days. The initial symptoms include cough, fever, dyspnea, and then followed by pneumonia in some cases (40).

The diagnostic procedure is based on positive laboratory tests for the virus, epidemiological history, clinical manifestation, and CT scan (41, 42). Huang et al., initially documented the clinical signs and symptoms of COVID-19 (8). They reported that hospitalized patients have a fever (98%), cough (76%), dyspnea (55%), most of them

developed dyspnea after eight days of first symptoms, 32% of them have relative hypoxemia so they needed ICU, but 10% required a mechanical ventilator (8). However, with the spreading of the virus globally, a range of other symptoms was reported such as diarrhea, vomiting, loss of appetite and abdominal pain (43). Regarding laboratory diagnosis, it is usually based on real-time-polymerase chain reaction (RT-PCR) because of higher accuracy than other methods such as serological tests and enzyme-linked immunosorbent assay (ELISA) however due to false-negative results, other mentioned criteria for diagnosis should not be excluded as occurred in the diagnosis of SARS-CoV-1 (44).

Disease management is one of the most challenging approaches faced by the health care systems. This is attributed to the lack of previous experience and the unavailability of drugs or vaccines, as COVID-19 is a new and different pandemic. Therefore, clinicians initially relied on supportive care, trying a variety of known antiviral drugs as repurposing agents that were used to treat other viruses such as MERS-CoV, SARS-CoV-1, Ebola virus, and others diseases (45). Varieties of repurposing immunotherapies have been tested for infected individuals until we have a proper randomized clinical trial (46, 47).

5. Immunology of SARS-CoV-2

Memory T cells initiated by prior microbes can make the immune system strong and memorize the infection to instantly attack the same pathogen. However, little is known about the human memory T cells in the SARS-CoV-2 that recognize the same agent. So, here we discussed the detailed immunological response.to COVID-19 infection.

4.1 Immune response to SARS-CoV-2

The detailed immune response of the virus is not fully understood yet, but it is believed to resemble other CoVs (48). After entering the cell employing endocytosis, the pathogen-associated molecules (PAMP) to the virus, stimulate toll-like receptors (TLR3 and TLR9) on the endosome. The virus may leave the endosome in the cytoplasm and stimulates soluble cytoplasmic pattern recognition receptors (PRR) (retinoic acid-inducible gene 1 (RIG-1), melanoma differentiation-associated protein 5 (MDA5) and nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) (49). After stimulation, the endocytic or cytosolic PRR, IFN regulatory factors (IRFs), and nuclear factor kappa-light-chain enhancer of activated B cell (NF-κB) will be phosphorylated and translocated to the nucleus to activate the part of DNA which is responsible for the production of IFNs (50). Type □ IFN includes IFN-α and IFN-β which are secreted by infected cell and act as paracrine bind to their receptor on the adjacent intact cells to activate Janus kinase-signal transducer and activators of transcription (JAK-STAT); the activated STAT1 and STAT2 form a complex with IRF9 which again translocate the nucleus to activate interferon-stimulated genes (ISGs) on the nucleus to yield a huge amount of antiviral proteins (51) (52). Type □ IFN includes IFN-ʎ also increases the antiviral state of neighboring infected cells through the same mechanism. Additionally, IFNs activate dendritic cells (DC), which in turn activate natural killer cells (NK) upon the secretion of IL-12; NK cells can kill and eliminate the virally infected cells (53). The TLRs recognize invading pathogens and activate the innate immune system. TLR plays a vital role in releasing pro-IL-1β when binds to SARS-CoV-2 infecting host. Pro-IL-1β is cleaved by pro-inflammatory protease caspase-1 which is activated by multi-protein complex; inflammasome. Consequently, pro-IL-1β

is converted into its active mature form. In extension to innate immune response, the adaptive immune response starts when the virus is processed and presented by infected cells and APCs to CTL and T_h cells, respectively. IL-12 increases the autolytic activity of CTL. IL-12 and IFN-γ can shift Th to Th1, which further activate CTL. During CoVs infection, B lymphocyte is also activated to generate antibody and memory cells (54). Beside cellular immunity of both arms of the immune response, humoral responses also play an important aspect to eradicate the virus. Humoral responses include an antibody, complement, and other soluble factors (55). The evidence for this antibody which formed in post-MERS-CoV infection can be identified (56).

Although immune response activates against CoVs infection, the CoVs still can induce infection because they have the mechanism to evade the immune system that may be scrutinized by decrease secretion of IFN-β via expression of the protein by orf3b and orf8 (57). Decreasing T lymphocyte by the CoVs is another mechanism of immune evasion which is more common in COVD-19 patients (58).

4.2 Cytokines and Immunopathogensis of SARS-CoV-2

The inflammation which develops during the severe immune response to CoVs like a double-edged sword that can kill the virus, but it also produces CS which culminates by lung damage and death (59) via increasing oxidative stress (60). In patients with COVID-19, there is an over-activation of immune responses (61). However, the hyperactive immune inflammation and systemic damage by SARS CoV-2 is yet to be determined.

The interaction of the virus with PRR also results in the production of a huge amount of pro-inflammatory cytokines, such as 1L-1β, IL-6, TNF-α (62), and chemokines such as CCL2 and IP-10 (63). These chemokines are capable of navigating macrophage,

neutrophil, T-lymphocyte, and NK to the target location of the infection. This induces a hyper-inflammatory state in severe cases of COVID-19 (59).

The inflammatory signature recorded in the blood of COVID 19 patients showed induction in the IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), IFN-γ, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), platelet-derived growth factor (PDGF), monocyte chemo-attractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), TNFα, vascular endothelial growth factor (VEGF) (8, 64).

Cytokine storm (CS) is the network of molecular events occurring due to excessive and dysregulated immune response to infection (65). It is manifested by excessive accumulation of inflammatory cells, complements, inflammatory cytokines, and chemokines (66). It usually occurs in severe cases of COVID-19 that leads to ARDS and DIC and multiple organ failure. IL-6, TNF-α, and IL-1β play a critical role in driving CS (67). The level of IL-6 is increased in patients infected by SARS-CoV-2, in which it makes a major contribution to tissue damage and inflammation. IL-6 contributes to atherogenesis, it plays a crucial role in the activation of coagulation after the elevation of thrombin-antithrombin III complexes and the prothrombin activation fragment F1 + (68). Moreover, coagulation is induced by IL-6 as a consequence of building hepatic of acute-phase proteins comprising of C-reactive protein (CRP), ferritin, and fibrinogen (69). Elevated concentration of IL-6 cytokine in COVID-19 patients can lead to DIC and multiple organ failure. D-dimer is one of the mediators of coagulation; Zhou *et al*. (2020) uncovered that the increased amount of D-dimer was observed in cases of SARS-CoV-2.

IL-1β also rises in COVID-19 which mediates lung, inflammation of the tissue, fibrosis, and fever (64).

TNF is a cell signaling inflammatory cytokine; it acts as an inflammation amplifier in every acute inflammatory situation (70). Blood and tissue samples of COVID-19 patients observed the presence of TNF molecules (71). The expression of adhesion molecules of lung capillary endothelial cells is increased by a pro-inflammatory TNF-α cytokine. Hence, the affinity of the neutrophil to adhere to the capillary endothelial cells is increased (72). The activated neutrophils secrets more chemokines; IL-8 that work with anaphylatoxin (C5a, C4a, and C3a) to provoke neutrophil recruitment to the capillary endothelial cells and then to migrate into the adjacent tissue (73).

The C-C motif ligand 2 (CCL2) is another chemokine released due to fusion of SARS-CoV-2 with ACE2 receptor (74). The CCL2 plays an important role in the migration of monocytes, memory T cells, and basophils and positioning them in tissues to participate in the inflammatory process (75). ARDS is an acute inflammatory lung injury that occurs in severe cases of COVID-19, which is characterized by pulmonary edema, hypoxia and opacification of the lungs upon CT scan (76). It usually develops after one week of the disease in some cases due to elevation of inflammatory cytokines, especially in elderly people (77). Elderly people, those with comorbidities, infected by SARS-CoV-2 tend to be more susceptible to initiate ARDS, which is in line with the death rates detected in older cases when compared with younger individuals (78). Among inflammatory cytokines, VEGF and TNF-α play a central role in driving ARDS (79). In addition, the level of VEGF is elevated in COVID-19 patients. In a study conducted by Kaner *et al*. (80), they stated that VEGF was overexpressed in the lungs, which can play a vital role in

the increase of pulmonary vascular permeability in the primitive stages of ARDS (80). TNF-α is raised in COVID-19 and it has also a role in pulmonary edema by up-regulating adhesion molecules and disrupting endothelial barrier in the blood vessels (81).

ACE2 is expressed in a wide variety of organs such as lungs, gut, kidney, cardiovascular and central nervous systems, as well as adipose tissues (82). Imai, Kuba (83) described the imperative role of ACE2 in the regulation of innate immunity. They have observed a more serious pulmonary inflammation in mice with deletion mutations of ACE2 prompted by acid aspiration compared with wild-type mice. These results can provide a notion that the inflammation could be more severe by the lowered ACE2 expression. The S protein in the SARS-CoV-2 envelope binds to the ACE2 surface protein to induce viral entry into the host cell and the virus also depends on TMPRSS2 as protease to cell entry (32). The latest investigations recognized ACE2 as a doorway “receptor” for the novel SARS-CoV-2 virus, hence, significantly associating inflammation and cardiovascular disorder (84). When SARS-CoV-2 binds to ACE2 receptor, the virus is endocytosed by the host cell and proteolytic cleavage process is activated; thus, the ACE2 losses its protective function (85). The ACE2 system provides a cascade of protection against pulmonary diseases, heart failure and diabetes mellitus (35).

Another detrimental effect of SARS-CoV-2 is the dysfunction of endoplasmic reticulum (ER), causing an ER stress response (86). The impaired folding of proteins in the lumen of ER has resulted in the aggregation of misfolded proteins; hence trigger the unfolded protein response (81), which maintains the homeostasis of endoplasmic reticulum organelles (87). Assuming that the ER stress is persisted and it is irreparable, the unfolded protein response (UPR) will trigger the apoptosis process (88). The induction

of ER stress response is activated in case of viral infections. The UPR acts as a defense mechanism against the virus and the protein synthesis is attenuated to minimize the burden on the ER (89). The level of protein entering the ER can fluctuate significantly under various physiological states and natural conditions. At the point when protein production enhances the folding and unfolding of stored proteins in the ER and lead to ER stress. Excessive lipid damage and pro-inflammatory chemokines lead to ER stress. To sustain homeostasis, cells are responsible for defensive signaling pathways known as UPR. UPR signaling pathways activate three vital stress transducers such as PKR-like ER protein kinase (PERK), enacting transcriptional factor-6 (ATF6), or inositol-requiring protein-1 (IRE1). Triggering of these sensors communicates the sign across the ER layer to the cytosol and the nucleus, however lower the function of these can lead to pathogenesis of SARS-CoV-2 (89).

The interaction between CoV and the host, induces the ER stress response and UPR activation. Different signaling processes are modulated through activation of the three branches of UPR; mitogen-activated protein kinase activation, apoptosis, autophagy, and innate immune response (90). Nabirotchkin, Peluffo (91) also reported that ER stress and UPR may participate in the pathogenesis of the novel SARS-CoV-2 virus, and concluded that the utilization of drug repositioning could be a good strategy to treat patients with COVID-19.

6. Immunotherapeutic strategies

Here, we focus on promising immunotherapies that increase immunity against SARS-CoV-2 or decrease inflammatory cascades since sometimes excessive inflammatory response occurs against the virus that leads to CS syndrome that eventually results in

coagulation abnormalities, as well as, respiratory, and multiple organ failure (92, 93). An immune-modulating therapy also called an anti-inflammatory agent which is used in hyper-inflammatory conditions. Generally, the prediction of healing from CS is unfavorable, hence identification and utilization of such repurpose medication may have a significant effect and probably reduce mortality (57, 94). The application of immunotherapeutic drugs that mostly act as an anti-inflammatory agent is challenging and the side effects of the drugs should be taken into accounts: first, anti-inflammatory agents decrease immunity that delays clearance of the virus and increase the chances of patient to secondary bacterial infection (95). Second, most immunotherapeutic drugs have a single or specific target, as they inhibit only one cytokine, which makes the inflammation difficult to control since inflammation is the result of multiple cytokines (96, 97). Third, some immunotherapeutics are not selective such as JAK inhibitors which may also reduce TNF-α level (98); the latter is very crucial in the removal of viruses (97, 99). Last but not the least, some immunotherapeutic should be used in combination with other drugs that counteract their side effects. For instance, corticosteroids increase the chance of bacterial infection by damaging the T lymphocytes (100) therefore, they should be used with antimicrobials; e.g., thymosin (101). The application of anti-inflammatory agents, besides their side effects, could survive the critical case of COVID-19 patients especially one or two weeks after onset of the disease due to CS (97, 102). Therefore, the application of anti-inflammatory agents provides a narrow window for those that their survival window is finite and will probably lead to the achievement of a more positive outcome (97).

5.1 NSAIDs

NSAIDs are anti-inflammatory agents that function as inhibitors of cyclooxygenase COX enzyme which are responsible for the production of inflammatory prostaglandins (Figure 1B). At the onset of the COVID-19 outbreak, there was contradictory information concerning the safety and effectiveness of NSAIDs (103).

The safety profile of NSAIDs was not good during SARS-CoV-1 infection because of two opposed actions. First, NSAIDs down-regulate ACE2 in the respiratory system that reduces pulmonary function (104). Second, NSAIDs up-regulate ACE2 especially in diabetic patients and patients that take ACE2 receptor inhibitors (such as losartan) (105), therefore, the over-expression of ACE2 receptors might facilitate the entry of SARS-CoV-2 and increases the chance of infection.

Some COVID-19 patients took acetaminophen or ibuprofen to reduce fever and pain, which are the manifestations of the disease. The impact of ibuprofen on human was shown in (Table 1). Michael Day established that the infected people should not take ibuprofen to reduce fever instead take acetaminophen because that ibuprofen might be an aggravating factor for the disease (106). As of 17th March, 2020, NHS medical practitioners in the UK announced CAS alert regarding using NSAIDs after worsening the symptoms of four COVID-19 cases as patients were taking these drugs without underlying other health problems (106).

Since May 2019, a review of ibuprofen and ketoprofen has been ongoing with signals that varicella infection and certain bacterial infections could be aggravated by these drugs (107). The Swedish health agency is against using NSAIDs randomly to treat COVID-19 symptoms, it explains that the anti-inflammatory and antipyretic effects can mask symptoms of a deterioration in the disease picture in infection (108). A study has shown

that ibuprofen in vitro inhibits peripheral blood mononuclear cells and IgM and IgG synthesis (109).

Indomethacin is another NSAID that is used for the treatment of gout and rheumatoid arthritis (110). The *in vitro* studies verified the efficacy of the drug in inhibiting the replication of the virus and reducing the damage caused by canine CoVs. It is also proven that the *in vivo* application of indomethacin in an infected dog is effective at a dose of 1mg/kg to combat against SARS-CoV-1 (110).

The ongoing clinical trials regarding consuming ibuprofen in COVID-19 patients in the UK and Argentina are NCT04334629 and NCT04382768, respectively. While, NCT04383899 is the clinical trial to know the side effects of ibuprofen in patients with COVID-19 among French people.

For decades, one of the most important problems in using NSAIDs is the panic that spread in the community due to their side effects including hypertension, renal problems, and gastrointestinal problems (111). Keeping in mind these reasons, there are few completed and ongoing trials concerning the use of NSAIDs in COVID-19 patients. If practitioners and researchers find the lowest safe effective dose of NSAIDs by their study to reduce the symptomatic treatment of COVID-19, it will be a good solution at that moment since there are no drugs and vaccines to overcome the disease. The justifications of not using NSAIDs are not too strong since the upregulation of ACE2 occurs during the chronic use of the drugs which make the person vulnerable to the disease. When the person is infected with the disease, the upregulation of the ACE2 receptor either will not happen strongly during the acute onset of the infection or will not affect the severity of the disease (112). Another justification is that the antipyretic property of the NSAIDs

reduces killing the virus by the body because clinicians believe that fever is the weapon to reduce replication of the virus (113). If this justification is true, it must be fulfilled over other antipyretic agents including acetaminophen. Finally, the evidence of the upregulation of ACE2 by the drug are originated from the animal models, they may not transferable to the human (114).

5.2 Corticosteroids

Corticosteroids are potent immunomodulators that suppress the immune system, so they are used to treat various diseases and inflammatory conditions. It is administered at a low dose to treat some cancer and auto-immune diseases in which inflammation is predominated (115). One should be cautious of prescribing corticosteroids for such individuals as they can be like a double-edged sword; this is for several advantages and disadvantages. This group of medication could be used in a CS and the hyper-inflammatory state as it could have both an immunosuppressant effect and an anti-inflammatory effect (116) (60). The above property could combat CS phenomenon in patients infected with COVID-19, such as ALI, ARDS, and coagulopathy status (3) (57).

The lethal effect of severe COVID-19 pneumonia is related to the pathological inflammatory reaction characterized by the destruction of deep airway and alveoli (117). Thymosin has been clinically used in patients with COVID-19 in adjunct to corticosteroids to reverse the side effects of corticosteroids (8).

However, some data from China demonstrates that in those patients with severe pneumonia, early introduction of a short course of low dose methylprednisolone could improve both clinical and radiological outcome (118). It has been documented that the

use of dexamethasone as supportive care for moderate and severe COVID-19 patients leads to a decrease in the duration of mechanical ventilator and mortality rate (Table 1) (119-120).

On the other hand, corticosteroid therapy has serious clinical complications. The most common adverse effects caused by corticosteroid are a secondary bacterial and fungal infection (121) (122). Hence, to overcome secondary infection in severe COVID-19 patients, clinicians should immediately add full-dose antibacterial drugs (118).

The use of corticosteroids are still controversial, however, Wang, Jiang (118). noticed no significant effect of glucocorticoid treatment on the outcome of approximately half of the infected patients with new CoVs. Also, Russell, Millar (123) studied the effect of steroids on COVID related lung damages and concluded no clinical evidence to support such therapy. In another study completed in China, where steroid treatment was observed to increase clinical symptoms, biomarkers, and radiological findings in young individuals (124). For the above reasons, the WHO is against the routine use of corticosteroids to treat pneumonia and ARDS in COVID-19 patients (12). However, in their last living guidance, WHO strongly recommends systemic (intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19 (1). Broadly speaking, according to the guidelines, corticosteroids are not given to the COVID-19 case without ARDS but its utilization for COVID-19 with ARDS is still used since the dose and the time of administration are not known (125). It needs time to adjust the dose in order not to delay viral clearance and not predisposing to secondary bacterial infection. Corticosteroids also need many clinical trials to know other

side effects including lymphocyte damage (126). Therefore, we highlight the attentiveness of using the drug while more research should be implemented to ensure the efficacy and safety of corticosteroid.

5.2 Monoclonal antibodies

5.3.1 IL-6 blockade

The IL-6 production is a response to both infection and tissue injury, which promptly contributes to the host defense via inducing acute phase proteins, hematopoiesis, and inflammation (63). Despite that IL6 expression is controlled by various mechanisms comprising the post-transcriptional and transcriptional process. Often its concentration is debilitating and contributes to multiple autoimmune disorders and inflammatory conditions (127). Based on its position, there are two types of IL-6 receptors (IL-6R): membrane-bound (mIL-6R) and a soluble form (sIL-6R), the latter binds to IL-6 to form a complex which binds to gp130 on the cell membrane to complete the signal transduction system and respond to infection via an inflammatory response (128). Further, the SARS-CoV-2 infection observations found an increase in inflammatory cytokines (129). Hence, the blockage of IL-6 could have a significant impact on reducing inflammation in COVID-19 patients.

Globally, the intensive care beds are limited and with the COVID-19 outbreak, such units will become overwhelmed with severe ARDS cases (130). To date, neither a vaccine nor specific antiviral therapy is available to combat novel CoV, therefore the administration of cytokine inhibitor especially IL-6 which has a role in hyper-inflammation could mitigate the severity of the disease (131) (132).

In addition to the immunological characteristics of COVID-19 patients in critical care, units have suggested hyper-activation of the humoral immune pathway, including IL-6 as a critical mediator for respiratory failure, shock, and multi-organ damage (133). This cytokine release syndrome that culminates in the release of a huge amount of pro-inflammatory cytokines must be under the tight control of immunological homeostasis and sometimes it is the target for immunotherapeutic (134). During the ALI, macrophage activating syndrome and ARDS result from CS that occurs when pro-inflammatory cytokines mainly IL-6 are released in huge amount so blockage of IL-6 is therapeutically important to reduce CS in COVID-19 patients (135).

Towards a drug, Tocilizumab (TCZ) is an example of mAb that acts as an IL-6 inhibitor that binds to both mIL-6R and sIL-6R (Figure 1C), it is used to treat RA to reduce inflammation. It has been approved to treat cytokine release syndrome followed chimeric antigen receptor -T (CAR-T) cell immunotherapy therapy in the United States since 2017 (97).

Xu & Han (136) reported in his retrospective study among 21 patients that administration of TCZ in severe cases of COVID-19 in the dose of 400 mg with a combination of antiviral therapy resulted in improvement of both the fever and oxygenation (75%) remarkably within few days. Apart from that, both the biochemical profile (peripheral lymphocytes 52%) and radiological opacifications (90.5%) improved. This research showed promised results that the application of this mAb might be beneficial in severe cases of COVID-19 (Table 1).

Lately, many clinical trials have registered to know the efficacy and safety of TCZ to relieve CS and pneumonia in severe cases of COVD-19. There are clinical trials

(ChiCTR2000029765), (ChiCTR2000030796), (ChiCTR2000030442) and (ChiCTR2000030894) that address the use of TCZ alone or in combination with other drugs to treat COVID-19 (97).

Sarilumab (Kevzara) is also another inhibitor of IL-6 that interferes with IL-6 signaling by binding to both mIL-6R and sIL-6R (Figure 1C), it is used for the treatment of RA. The "NCT04315298" is the identifier for the clinical trial which has been launched in the United States to know the safety profile of Sarilumab in COVID-19 cases.

Siltuximab (Sylvant) is another IL-6 antagonist that also binds to both types of IL-6R (Figure 1C), it is approved since 2014 by FDA to treat multicentric Castleman's disease which is a rare disorder characterized by hyper-inflammation (137). Gritti, Raimondi (138) found that siltuximab administration leads to a reduction of both CRPs via inhibition of IL-6 in COVID-19 patients (Table 1).

IL-6 blockade agents, that act as immune-modulators, besides their advantage for decreasing inflammation in CS of COVID-19, delay viral clearance; this problem can be tackled by combination with antiviral drugs. They also increase vulnerability to a secondary bacterial infection which can be prevented by their administration with antibiotics. It is also important to address the number for scaling severity of disease and determine the number (the time) when these immune-modulatory agents can be applied. This can be achieved by the measurement of CRP and IL-6 in COVID-19 patients.

5.3.2 Leronlimab (Pro 140)

Leronlimab is another mAb that is based on IgG4 to treat various diseases including AIDS, metastatic cancer, and nonalcoholic steatohepatitis (NASH) which exhibits inflammation. It is chemokine receptor 5 (CCR5) antagonism (Figure 1C), CCR5 is a chemokine that recruits leukocyte to the site of inflammation (139), it is reported that the deletion of CCR5 protects against inflammation (140). The FDA has authorized and approved the starting of a new stage 2 trial to analyze the benefits and purposes of leronlimab in the treatment of patients which are dealing with weak to average respiratory complications who have been diagnosed with COVID-19 (141). CytoDyn, The developer of Leronlimab "CytoDyn", informed in a media publication that in their trial of treatment with leronlimab; after 3 days of treatment 8 patients with COVID19 who were severely sick, presented development in various significant immunologic biomarkers, comprising of cytokines, IL-6, and an aim in approaching the normalization of the CD4/CD8 proportionality (139) (Table 1).

Glass and Lane (142) showed that the blockage of CCR5 restores the INF-γ and CD+4/CD+ ratio during SARS-CoV-1 infection (142). CCL5 is a chemokine that binds to the CCR5 receptor thereby it drives inflammation. The blockage of this CCL5-CCR5 axis by leronlimab has a role in mitigating the disease. Leronlimab 's safety profile is not clear yet since CCR5 that expresses on CTL has a role in driving it to the affected area and increasing the antiviral activity. It was expected that leronlimab besides anti-inflammatory effects, delayed viral clearance, however, a recent study revealed that the application of corticosteroids did not affect viral clearance time and length of hospital stay in mild COVID□19 cases (80).

5.3.3 Bevacizumab (Avastin)

Pulmonary edema is the foremost harm, causing characteristics of ALI/ARDS which are the main complications of SARS-CoV-2 infection (143). The results of the postmortem autopsy form COVID-19 cases recorded that there was pulmonary edema that was more serious and more noticeable than the SARS infection. Therefore, pulmonary CT scanning and pathological data can likewise conclude that inflammatory exudation which causes pulmonary edema is the main distinguishable factor of COVID-19 (117). Nonetheless, special pharmacotherapy is still needed. VEGF is the strongest and most effective inducing aspect to enhance vascular permeability and induces angiogenesis. It is released in cases of hypoxia. Bevacizumab is a VEGF antagonist widely being used for the treatment of various cancers (144). Bevacizumab works by blocking VEGF and thus preventing it to bind with its receptor (Figure 1C), consequently the formation of new vasculature and vascular permeability is rendered. Therefore, the application of Bevacizumab may be a favorable medicine for serious and extreme COVID-19 cases. “NCT04305106” is the clinical trial, titled as, “application of Bevacizumab in severe cases of COVID-19 patients”.

“NCT04305106” and “NCT04275414” are the clinical trial titles application of Bevacizumab in severe cases of COVID-19 patients.

All things considered; bevacizumab is important to reduce pulmonary edema that accompanies SARS-CoV-2 infection. Its effective dose and safety profile should be revealed in the clinical trials since the drug has a long half.

5.3.4 Adalimumab (Humira)

It is anti-TNF-α mAb that prevents TNF-α from inducing its inflammatory response which is used for the treatment of RA, irritable bowel diseases, and ankylosing spondylitis (145). The TNF-α inhibitors reduce capillary leakage by reducing the expression of the adhesion molecule and VEGF (146). It also reduces inflammatory cytokine (IL-1 and IL-6) in RA (147). The TNF-α has a role in many inflammatory driven diseases including COVID-19 (115). Diao, Wang (148) demonstrated high levels of TNF-α were seen in patients diagnosed with COVID-19. Russell, Moss (115) established that TNF-α inhibition in COVID-19 cases is safe. Therefore, the application of Adalimumab enrolls in two clinical trials: "ChiCTR2000030089" and "ChiCTR2000030580". Recent studies suggested that COVID-19 patients taking Adalimumab or other anti-TNF for other diseases are less likely to be admitted in hospital.

Altogether, TNF-α inhibitors may improve severe symptoms of COVID-19 because they decrease other potent inflammatory cytokines that are responsible for CS beside TNF-α. It is better to be given directly after hospitalization before CS begins. Because of its strong anti-inflammatory effects, further clinical trials should be done to assure its safety profile; it may prone the patients to secondary bacterial infection since bacterial superinfection is common during viral infections.

5.3.5 Emapalumab (Gamifant)

IFN-γ is an inflammatory cytokine and possesses many biological activities (149). It can enhance the major histocompatibility complex (MHC) expression, activate macrophage function, stimulate chemokine production; its products can be up-regulated by the chemokines IP-10, which is found to be significantly increased in severe cases of SARS. The IP-10 levels are extremely high and it seems to be a more reliable marker for viral infection, which have documented in SARS-CoV-1 (150). Huang, Su (151) noted that IFN-γ related CS was found in SARS-CoV-1 infection which might be involved in pulmonary damage of SARS patients (151).

Emapalumab is humanized mAb with IFN-γ antagonistic property (Figure 1C), it is approved in the United States for treatment of primary hemophagocytic lymphohistiocytosis (HLH) if the disease doesn't respond to its primary treatment (152). It is effective for that disease which is its hyper-inflammation overwhelmed by activation of T cell and macrophage. However, there is no evidence for the contribution of IFN-γ in CS of COVID-19 (153). It is proven that emapalumab decreases CXCL9 which is the chemokine that polarizes T_{h1} (154). In addition, CXCL9 upregulates RORγt that polarizes toward T_{h17} (154) which is believed to play a detrimental role in COVID-19 (156). "NCT04324021" is an ongoing clinical trial on using a combination of emapalumab with anakinra to treat CS in COVID-19 patients.

5.3.6 Complement (C) inhibitors

The complement, especially C5 and C3, has a detrimental role in driving inflammation in COVID-19. The C5a is elevated in COVID-19 patients based on research done in China, so clinical trials with antibodies that inhibit C5a are conducted (5). One explanation for the contribution of C5a in SRAS-CoV-2 mediated inflammation is for its chemotaxis

effect that recruits macrophages and neutrophils to the site of infection. Thrombotic microangiopathy is caused by various reasons in COVID-19, and one of the scenarios is SARS-CoV-2 mediated complement activation. The SARS-CoV-1 murine model with a lack of C3 showed decreased severity of the disease and organ damage (157). MERS-CoV murine model with C5a inhibition showed decreased levels of cytokine, viral load, and lung damage (158). Today, antagonists of C5 and C5a are approved by the FDA for the treatment of complement related disorders. C5a antagonists have a better safety profile than C5 because it does not inhibit membrane attack complex (MAC) formation and hence does not weaken the immune system's ability to kill the virus.

Eculizumab (Soliris) and ravulizumab (Ultomiris) are mAbs approved to bind to complement factor C5 and prevent the formation of MAC (Figure 1C). They affect the complement system, which may help to minimize organ damage in severe patients. These drugs were first FDA listed for paroxysmal nocturnal hemoglobinuria, which is the rare disease of the blood and later for hemolytic uremic syndrome and myasthenia gravis (159) (160). “NCT04288713” is a clinical trial underpinned the use of eculizumab in SRAS-CoV-2 related CS.

Another drug engineered to suppress C5a biological activity is IFX-1 which is also a monoclonal anti-human complement factor C5a antibody designed to inhibit the biological activity of C5a (Figure 1C). The drug is not thought to affect MAC formation (C5b-9). It can regulate the tissue and organ damage associated with the inflammatory response through a C5a selective blockade. IFX-1 is under consideration to treat inflammatory conditions (161). The clinical trial for therapeutical application of INFX-1in severe COVID-19 cases have been registered as "NCT04333420”.

In COVID-19, activation of C3 is responsible for inflammation as part of an innate immune response contributing to coagulopathy and organ failure (162). Hence, in critical cases of COVID-19, C3 inhibition can provide an opportunity to inhibit complement-mediated inflammatory reactions. Compastatin Cp40 / AMY 101 is a potent selective C3 inhibitor used in complement-induced disorders such as ARDS (163), which is one of the COVID-19 cases' fatal complications (Table 1).

Additional questions must be answered before using C5a, C5, and C3 inhibitors such as what is the time window for drug intervention? What are the indicators for increasing complement during SARS-CoV-2 infection? It is clear that there is not a routine indicator for complement activation; we must depend on alternative routine indicators that mirror increased complements such as CRP, ferritin, and IL-6.

5.3.7 Nivolumab (Opdivo)

Zhang, Zhao (97) found that functional exhaustion of antiviral lymphocytes occurred in COVID-19 patients. This depresses of functional activity of T or NK cells are due to immune checkpoints such as programmed death receptor-1 (PD-1). Chiappelli, Khakshooy (164) reported that PD-1 over-expressed in COVID-19 patients, therefore, checkpoint inhibitors like anti-PD-1 would be helpful.

Nivolumab (Opdivo) is a fully human monoclonal PD-1 antibody that functions as a negative regulatory checkpoint molecule in immunosuppression (165) (Figure 1C). “NCT04333914" is a clinical trial in COVID-19 patients that combined this drug with chloroquine analog (GNS561) and tocilizumab.

In short, PD-1 inhibitors are important to abrogate the exhaustion of CTL which is responsible for killing the virus. At the same time, they may produce immune hyper-activation that may exacerbate lung damage in COVID-19 patients. However, Immune hyper-activation is not a common side effect of PD-1 inhibitors but clinical consideration should be taken during administration of them. Side effects of these drugs may synergize with the pathogenesis of SARS-CoV-2 in immune hyper-activation and CS leads to fatal outcomes.

5.4 Interferons (IFNs)

IFNs are a group of cytokines with antiviral properties by inducing the intact neighboring cells to release molecules that interfere with viral replication. They increase the autolytic activity of NK and macrophage against the virus. There are three families of IFNs: type □ (IFN-α and IFN-β), type □ (IFN-γ), and type □ (IFN-λ) (166). Type □ IFNs have the main role in the eradication of CoVs (SARS-CoV-1 and MERS-CoV) (167). So, they are used as a treatment to combat CoVs and hepatitis B virus (HBV) specially IFN-α but it produces many systematic side effects such as depression of bone marrow, production flu-like symptoms, increasing suicidal ideas. Currently, there are many attempts to replace IFN-α with safer IFN-λ which has fewer side effects. IFN-λ or IFN-γ has less antiviral activity if compared to type1 IFNs, so they are used synergistically with low doses with IFN-α to increase antiviral activity and decrease side effects of them (168). The CoVs have strategies to evade the immune system, one of these strategies is to reduce type1 IFNs to dampen the immune system and spread easily from one cell to another (167).

Larkin, Jin (169) underpinned that a combination of IFN-α and IFN-γ in vitro provided strong synergistic antiviral activities at much lower dosages of IFN than normally required. Lowering the dose of IFNs in combination therapy offers the advantage of the reduction in undesired side effects for the patients. Nagata, Iwata (170) have described the destructive effect of CS in adult mice after SARS-CoV-1 infection, while IV injections of TNF-α were not beneficial, intraperitoneal IFN-γ injection showed a protective effect. Cinatl, Morgenstern (171) reported the in vitro superiority of IFN-β over -α and -γ while suggesting the effectiveness of IFN-γ over IFN-α in Vero cell cultures of SARS-CoV-1 infection. Scagnolari, Vicenzi (172) also reported the synergistic effects of IFN-γ and -β on Vero cells infected with SARS-CoV. Another study established that IFN-α and IFN-γ co-administration caused hyper-activated IRF-1 and STAT1, which lastly resulted in a more vigorous antiviral activity replication of viruses (173).

Although IFNs are available as medicinal products, some adverse effects should be considered for their direct indication. Moreover, the protocol for their indication including proper timing and dosing should be confirmed (174).

Shen and Yang (175) believe that the treatment of COVID-19 patients with IFN-α and IFN-β show promised results since SARS-CoV-2 is more sensitive to these IFN as compared to SARS-CoV-1. To confirm this idea, infected patients were sprayed with IFN-α2b and found to infected patients, he saw that the infection rate with SARS-CoV-2 would be decreased. Another study reported that this type of treatment can also be utilized for prophylaxis of the disease (176). Sheahan, Sims (177) reported that a

combination of type 1 IFN with potential repurposes antiviral drugs such as lopinavir/ritonavir, remdesivir, and ribavirin could yield better efficacy (Table 1).

The administration of IFN-α2b in five mU twice daily in inhalable form is the guideline used by the physician in China (178) (5). There are many clinical trials regarding the use of IFN in COVID-19 either alone or in combination. Zhou et al conducted a research on 77 COVID-19 patients in China for 11 days (median times), they used IFN-α2b 5 mU twice daily in respirable form with and without umifenovir 200 mg three times daily for the patients, and revealed that this treatment is effective for reducing viral load and inflammatory markers (CRP and IL-6) (179).

"ChiCTR2000029387" is the clinical trial that is designed to use IFN-α2b in combination lopinavir/ritonavir (178) (5) "NCT04276688" is another clinical trial for subcutaneous application of IFN-β1b in combination with lopinavir/ritonavir and ribavirin for COVID-19 patients. "NCT04331899" is a clinical trial that claims to use III IFN (Peginterferon) in mild cases in the United States. "NCT04315948" is the trial that compares a combination of IFN-β1b and lopinavir/ritonavir with other repurposed drugs (180).

Generally, the physicians are waiting for the results of clinical trials to know the exact dose, time of administration, and the side effects of IFNs. It is also essential to determine in which phase, IFN must be given since IFN administration has flaws, such as the pulmonary lesions which are also more predominantly in the second phase. Therefore, IFN treatment in this phase may produce interferonopathies and exacerbate pulmonary lesions. Conversely, the pulmonary lesions are less significant in the early stage, so its administration may be effective in this stage but it does not mean that IFN is not used in

the third phase (hyperinflammatory state), all of these uncertainties must be proved in the clinical trials.

5.5 Convalescent plasma

There is an old, yet new, the strategy of immune therapy to prevent or cure viral and bacterial infections (181). It includes the collection and utilization of antibodies from the plasma of recovered patients who have developed humoral immunity against the same disease' causative pathogen. The antibodies-based immune therapy offers a proximate immunity to the patients. At present, it is a more beneficial approach to target SARS-COV-2 than the prophylaxis vaccination, since it doesn't require a long time to prepare and validate before treating the patients. Unlike the distinct targeted mAb therapy, the convalescent plasma contains neutralizing antibodies that prevent the viral duplication and/or virus-human cell bindings. Apart from the neutralization effect, the antibodies may induce antibody-dependent cell-mediated cytotoxicity (via NK cells), complement induced cytotoxicity and phagocytosis (182)

During the last two decades, plasma containing antibodies have been used to treat different pandemics such as SARS, MERS, and Ebola virus. Despite that, the approach wasn't so effective and promising with the Ebola virus (183). the strategy was more pronounced with SARS and MERS, as observed via a significant reduction in death rates when compared to the non-treated group (184). Some papers and trials have been testing the effect of convalescent plasma on COVID-19 patients. The effect was prominent, and the safety of the treatment was reported, however, the sample size included in the study was relatively small (Table 1). Yet, there are no specific regulations to collect and use the

convalescent plasma from recovered COVID-19 patients worldwide; however, the FDA organization issued few recommendations for regulated investigational purposes. The donor should be a COVID 19 confirmed and recovered patient, who has been 14 days of disease-free confirmed via a serological or molecular test. Additionally, the antibody titer test should be performed before the donation, where the neutralizing antibody titer of 1/160 is required (185). Like other treatment strategies, the convalescent plasma has some risks; such as the one which is related to the blood transfer that may get an accidental infectious disease or the one which is attributed to serum sickness. Other risks may be justified by the concept of antibody-dependent enhancement of infection, especially if the donor plasma has a lower titer of neutralizing antibodies (186). In such a case, the treatment would induce an adverse effect and enhance the infection severity (187).

To highlight, the absence of scientific proves and the unavailability of standardized protocols for the correct doses and therapeutic management, plus the diversity in the nature of infection among different people, make this mode of immune therapy for COVID 19 limited relatively.

5.6 JAK inhibitors

Janus kinases (JAKs) consist of a family of intracellular tyrosine kinase (TYK) enzymes that phosphorylate and alter the activity of tyrosine hydroxyl residues in their target proteins. JAKs compromise four family groups of enzymes: JAK1, JAK2, JAK3, and TYK2. JAK3 is mainly present in hematopoietic cells, while kinases JAK1, JAK2, and TYK2 are ubiquitous. Numerous cytokines, such as ILs and IFNs, and hormones such as

erythropoietin, thrombopoietin, and growth hormone trigger JAKs. Binding a cytokine to its receptor causes activation of JAKs associated with that receptor and eventually results in phosphorylation of STATs, that is, activation of STATs. Phosphorylated STAT dimers translocate to the nucleus, where they regulate the expression of hundreds of proteins involved in the immune response and contributing to inflammation (188). JAK inhibitors are used for treating many diseases: RA, irritable bowel diseases, and many skin disorders.

5.6.1 Baricitinib

Baricitinib (Olumiant) is JAK inhibitor that works by inhibiting JAK1 and JAK2 enzymes (Figure 1C). It has been proposed as a potential candidate for COVID-19 therapy, taking in to account its relative safety and high affinities. A therapeutic dosage of either 2 mg or 4 mg once daily was enough to achieve inhibition plasma concentration. The biggest concern about JAK inhibitors, however, is that it can inhibit several inflammatory cytokines like INF-α, which plays an important role in curbing virus activity. To validate their effectiveness further clinical trials and studies are done (189) (Table 1). Another mechanism of baricitinib is inhibition of an adaptor protein complex (AP2)-associated protein kinase (AAK) which has the main role in clathrin-mediated endocytosis of the virus. AAK1 inhibitors can block the virus passage into cells and can help to avoid virus infections (190) (Figure 1C).

The other major viral input factor is endocytosis. Baricitinib is commercially available for RA and in clinical development for irritable bowel disease as a JAK1, JAK2, and TYK2 inhibitor and can inhibit endocytosis. This effect does not occur with the less selective JAK inhibitor, Tofacitinib (Richardson, 2020).

5.6.2 Ruxolitinib (Jakafi)

Ruxolitinib, another JAK1 and JAK2 inhibitor, is used as therapeutics for many inflammatory conditions: autoimmune diseases (191) and graft versus host disease (GVHD), which are resistant to corticosteroid therapy (192). Its ability to activate regulatory T lymphocyte (T_{reg}) can be considered as another mechanism for its immunosuppress activity (3). Its side effects can be explained by inhibition of JAK enzyme in the NK cell in which the cell does not respond to IL-12, IL-2 and IL-15 activation and maturation that consequently results in decreasing TNF-α and INF-γ which affects the maturation of DC and polarization T_{h1} negatively (193); the whole process can be scrutinized by decreasing the antiviral activity of NK and CTL and delay viral clearance in COVID-19 patients. These side effects were well underpinned in myeloproliferative neoplasm (MPN) patients during taking ruxolitinib (194). “ChiCTR2000029580" is the clinical trial that addresses the use of ruxolitinib in combination with stem cells to treat SARS-CoV-2 infection. NCT04331665 is another clinical trial that tests ruxolitinib for the treatment of COVID-19 to know its efficacy and safety. Table 1 provides further results from research on the use of this drug in COVID-19 patients.

5.6.3 Tofacitinib (Xeljanz)

It is also JAK inhibitor that when given orally, it is an inhibitor of JAK1 and JAK3 in a small dose (5 mg) and inhibitor of JAK2 in a larger dose (10 mg or above), but does not affect the AAK2 and clathrin-mediated endocytosis (195). So, it has fewer side effects if compared to other biological agents that are termed biological disease-modifying anti-

rheumatic drugs (bDMARDs) that subject patients to other infections (196). It is approved by the FDA and the European Medicine Agency (EMA) for treatment of RA with or without methotrexate for those who don't tolerate other bDMARDs (197, 198), it is also used for the treatment of irritable bowel disease (199).

The detailed mechanism of anti-inflammatory properties are due to its capacity to bind to adenosine triphosphate (ATP) binding site of JAKs which makes them irresponsive to multiple cytokines: IL21, IL-4, and IFN-γ (200) and IL-6 have a major role in enhancing inflammation in COVID-19 patients (201).

5.6.4 Jakotinib

Jakotinib dihydrochloride monohydrate is also a potent JAK1 and JAK2 inhibitor that is in the clinical trials for the treatment of myelofibrosis, alopecia areata, and pulmonary fibrosis, amyotrophic lateral sclerosis (14) (202). (ChiCTR2000030170) is the clinical trial for using jakotinib hydrochloride to treat severe cases of COVID-19.

In general, the side effects of JAK inhibitors should not be overlooked. They may aggravate coagulopathy which is found in some COVID-19 cases as FDA warns the experts who use JAK inhibitors. They might re-activate some latent viruses such as the herpes zoster virus. Likewise, they could decrease the response of some antiviral cytokines (such as IFN) or some immune-boosting cytokines (IL-2 and IL-7).

On balance, the inhibitors of a selective single cytokine such as tocilizumab and anakinra may not be effective to treat CS, since it is the result of multiple cytokines. It is hypothesized to use multiple cytokine inhibitors especially JAK and TYK inhibitors because they can attenuate many inflammatory cytokines that are responsible for the

formation of CS. JAK inhibitors which work on JAK1 and JAK2 are important therapeutically to treat COVID-19. Those inhibitors reduce IL-6 which is the main contributor to CS. However, the utilization of JAK and TYK inhibitors are not free from drawbacks, since JAK and TYK are shared by other cytokines (IL-2, IL-12, and IFN-γ), so blocking them by inhibitors; they may decrease the antiviral activity of CTL and NK cell. JAK inhibitors produce anemia because it is also signal transductors of erythropoietin hormone. JAK inhibitors are contraindicated in pregnancy, breastfeeding, and those who are in high blood clot risk.

5.7 Anakinra (Kineret)

Infection of the upper and lower respiratory tract with SARS-COV-2 can cause a mild or extremely severe respiratory syndrome with the release of inflammatory cytokines such as IL-1. Binding of SARS-COV-2 to the TLR induces the releases of pro-IL-1 which is cleaved by caspase-1, accompanied by activation of inflammasome and production of active mature IL-1 development which is a mediator of lung inflammation, fever, and fibrosis. It has been shown that the suppression of pro-inflammatory members of the IL-1 family has a therapeutic impact in many inflammatory diseases, including viral infections (129).

Repression of IL-1 has been shown to help many inflammatory diseases, including RA (105). It is well known that overexpression of IL-1 is considered to be characteristic of SARS-CoV infection, likely by activation of the transcription factor nuclear factor, activator protein 1, and activating factor 2.

The approved anakinra which treats CAPS (cryopyrin-associated periodic syndrome), RA, and still's a disease, represses the IL-1 biological activity by binding to the IL-1 type 1 receptor (Figure 1C), expressed in a wide range of tissues and organs (209). Another target for ankinara is neutrophil extracellular traps (NETs), which are formed to destroy the virus by active neutrophils. NETs are considered one of the risk factors in COVID-19 mediated CS to induce coagulopathy (210). Anakinra has two characteristics that make it the drug of choice for tackling COVID-19 related CS: first, it rarely produces opportunistic bacterial infection; second, it has a short half-life (3 hrs) this allows for the prompt stoppage and clearing from the blood (211-213). NCT04324021 emphasizes the utilization of the anakinra with emapalumab in COVID-19. Table 1 indicates more findings of studies on the use of this medication in COVID-19 patients.

To sum up, the IL-1 has a critical role in causing ARDS and CS which secondary to SARS-CoV-2 infection, so its inhibition by anakinra may yield a promising result. However, the safety profile is proven by some researchers but because of the small sample size we cannot guarantee its safety; the conduction of a study with a large sample size is recommended

5.8 Other miscellaneous agents

5.8.1 Thymosin

There are several immune modulators and drugs which can be tested and used to treat COVID 19. Among them is thymosin, which is a polypeptide hormone secreted by thymus cells, it has different forms, among them the $\alpha 1$ and $\beta 4$ are chemically synthesized. It plays a vital role in immune stimulation and homeostasis and has been

used in the treatment of different immunodeficiency diseases and cancer (214). Thymosin' broad action as an immunomodulator (via direct interaction with TLRs on DCs), activating different subsets of T-cells (CTL, T_h, and T_{reg}), inducing NK cell activity and many others (215) (Figure 1C). Among the different immune actions, thymosin reduces effectively the proinflammatory CS phenomenon, suggesting it as a promising therapeutic candidate for targeting SARS-COV-19. The immunological picture of COVID-19 patients may determine the relevance of such treatment, whether they are lymphocytopenic and have massive inflammatory responses (Table 1).

On the other hand, methylprednisolone has been widely used during the current COVID‐19 epidemic and the side effect of corticoid‐induced death of thymocytes should be considered (216). So, it is suggested to use thymosin α1 before methylprednisolone administration (217).

Yet, no studies have been reported for the uses of thymosin to treat COVID 19, therefore we would like to highlight the importance of investigating its therapeutic action against COVID-19.

5.8.2 Fingolimod

Other immune modulators, such as a sphingosine-1-phosphate receptor (S1PR) inhibitor (fingolimod), have been already on a single clinical trial (NCT04280588) in China without any reported results yet. The fingolimod (used to treat multiple sclerosis) is an immune modulator that prevents the lymphocyte from migrating outside the lymph node (Figure 1C). Such treatment can be combined with other treatments and should specify a specific type of patient who suffers from some immunological diseases (218).

Modulation of S1PR by fingolimod abrogates asthma by depresses bronchial contraction, changing DC function, and down-regulating the expression of cytokines (IL-6 and IL-8) (219, 220).

By and large, fingolimod may improve the pulmonary edema in ARDS of COVID-19 cases which are produced by chemotaxis of inflammatory cells including lymphocyte. Its safety must be confirmed by clinical trials since fingolimod approved by FDA to treat relapsing-remitting multiple sclerosis (RRMS), it produces severe lymphopenia.

5.8.3 Pirfenidone

Pirfenidone (Esbriet), is an anti-inflammatory and anti-pulmonary fibrotic drug that targets IL-1β and IL-4 and has an anti-oxidant effect. The efficacy of such a drug should be evaluated against COVID-19, this is because most of the patients suffer from lung fibrosis as well as its anti-oxidant effect can be useful for reducing the recorded coagulation effect of the virus. Currently, there is a running clinical trial (NCT04282902) in China, where the drug is used in combination with other drugs aiming at reducing the rate of infection among different patients (221).

To a great extent, applications of anti-fibrotic treatments are essential to mitigate pulmonary fibrosis which is secondary to SRAS-CoV-2 infection. When it is used, it will reduce pulmonary fibrosis in SARS-CoV-2 survivors, so it helps the recovery of the lung after viral infection.

5.8.4 CD24Fc

CD 24 extracellular domain-IgG1 Fc domain recombinant fusion protein (CD24Fc) is composed of heat-stable mucins like CD24 and Fc portion of IgG1 which are linked

commercially. The former is a receptor on hematopoietic cell (B, T lymphocyte and macrophage, DC) and non-hematopoietic cell (neuronal cell), has a role in hematopoietic and neuronal differentiation; it is also an immune check inhibitor has a role in cancer and autoimmune disease (222). Its anti-inflammatory effects belong to two actions: first, it prevents binding DAMP to PRR (e.g TLR), and second, by interacting with sigelcs G/10 forms a complex that blocks the signal transduction pathway of TLR (223). By these two functions, the CD24Fc can prevent the formation of NF-KB and pro-inflammatory cytokines compromising IL-6 and IL-1(223) (Figure 1B).

CD24Fc, an immune checkpoint inhibitor, is commercially prepared and it is in clinical trials to treat many disorders such as RA, multiple sclerosis, and GVHD. Phase of clinical trials of CD24Fc was recently started to be given to leukemia patients after bone marrow transplantation to prevent GVHD. NCT04317040 is the clinical trial for using CD24Fc as supportive care to treat COVD-19 patients.

5.8.5 Tranilast

Tranilast, a tryptophan like molecule, acts as anti-histamine and anti-inflammatory effects through many mechanisms (224): it blocks the release of histamine from mast cells (225), it blocks the formation of inflammatory prostaglandins via inhibiting COX2 in fibroblasts and macrophages (226, 227) and it decreases the release of IL-6 from endothelial cells (228). It is a potent inhibitor of NLRP3 which is an inflammasome that drives inflammation in many disorders including bronchial asthma (229) (Figure 1B). Tranilast represses fibrosis by inhibition of fibroblast activity (230) and collagen formation via reducing the activity of TGF-β (231). It has been proved that it mitigates the pulmonary fibrosis in experimental animals (232).

Because of anti-inflammatory and anti-fibrotic properties, it is believed to be useful to tackle the COVID-19, for this purpose clinical trial “ChiCTR2000030002” claims to use tranilast in SARS-CoV2 driven inflammation.

5.8.6 Cytokine based therapy

Cytokines are a group of glycoproteins that control many physiological hemostasis in the body comprising inflammation, hematopoiesis, and tissue remodeling and repair, but those which connect function between two arms of the immune system (non-specific and specific) are the most importance (50).

Interleukin-2 (IL-2) plays a central role among cytokines since it has pleiotropic roles including the proliferation of T lymphocyte, enhances the production of the memory cell, and controls the polarity of T_h to T_{h1} (50). Its anti-inflammatory propriety is due to the expansion and stabilization of T_{reg} cell that induces immunological tolerance which is very important in decreasing the inflammation in post-viral infection (233) (Figure 1C). Its antiviral activity belongs to its ability to expand viricidal immune cells (CTL and NK) (234) and stimulate the formation of a memory cell for CTL (235). One of the major obstacles that we face in the administration of IL-2 is short half-life and it is degraded shortly after being administrated so it must be given with monoclonal antibody (JES6-1) which attaches to IL-2 in the body and thus its destruction is prevented (233). If it is given at a low dose, it can control persistent viral infection (236) via the formation of the memory cell of CTL (237). In chronically infected mice, administrated IL-2 can increase expression of CD 44 and CD 127 in CTL memory cell; it can eradicate the virus (238).”

ChiCTR2000030167" is the ongoing clinical trial that aims to use IL-2 to strengthen CTL against SARS-CoV2 and control inflammation.

GM-CSF is a hematopoietic growth factor that stimulates the production of macrophages at low doses then followed by granulocytes by increasing the dose. It is also an immune-modulator (239). The therapeutic recombinant rh-GM-CSF can be given to the disease in which the leukopenia is common to prevent secondary bacterial infection (240). It stimulates the ability of macrophages to kill parasites (241). "ChiCTR2000030007" titles the clinical trial aims to reverse leukopenia which sometimes occurs in post-SARS-CoV2 infection.

Viral macrophage-inflammatory protein (vMIP), a virus-based protein, is produced by HHV8 as an evading mechanism to protect itself from T cell inflammatory driving killing. Therapeutically, we can get benefit from it to control inflammation because it is a strong chemokine antagonism by inhibiting CXCR4 receptor (242) (Table 1) (Figure 1C). ChiCTR2000029636 is the identifier of a clinical trial that is going to be given in the inhalator form to COVID-19 to know its safety and efficacy.

5.8.7 Adoptive cell therapy

NK cell is one of the adoptive based cell therapies, which are given to COVID-19 patients. It is manufactured by Cellularity Company from the human placenta. The FDA permitted investigational new drug (IND) therapy to use allogeneic NK cell named CYNK-001 in COVID-19 patients since NK cell can combat SARS-CoV2 by many ways; it can kill the virus directly by granzyme and apoptosis receptor (244), stimulates the activation of macrophage, triggers to shift polarity of T_h to T_{h1} (245) thereby it can activate CTL that kills the virus. CYNK-001 can also induce the formation of the long-

lasting memory cell and humoral response (243). National Research Project for SARS (246) found the number of NK cells lower in SARS patients compared to control, so it is believed that the administration of CYNK-001 could be a beneficial treatment in COVID-19 patients. NCT04280224, ChiCTR2000030329, and NCT04324996 are examples of clinical trials on the administration of NK cell which are started or going to begin soon.

T cell immunotherapy is another cell-based therapy to fight SARS-CoV2, the virus that leads to COVID-19, it is manufactured by AlloVir conjointly with Baylor college of medicine to fight SARS-CoV1, MERS-CoV, and SARS-CoV2. This kind of therapy may find the key to treat COVID-19 since T cell deficiency are more common in these viral infections (247).

Pluristem (PLX) is an allogeneic mesenchymal-like stem cell that decreases CS by activation of T_{reg} and M2 macrophages which decrease inflammation that accompanies COVID-19; PLX is now used by researchers in Israel for treatment of COVID-19 patients (248) (Table 1) (Figure 1C).

5.8.8 Thalidomide

It is a glutamic acid derivative that was previously used as anti-histamine and sedative agent in many allergic conditions, nausea, and vomiting during pregnancy (NVP) in pregnant women since it caused many limb deformities in newborn infants, and was withdrawn from the market (249). Importantly, now it is introduced to the market to other indications compromising anti-cancer and anti-inflammatory agents because it is a good inhibitor of many pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α (250) (Table 1) (Figure 1B).

It has previously been documented that the utilization of this drug combined with some antiviral drugs showed an excellent result to treat a severe case of H1N1 (251). It is also found that uses of this drug with corticosteroids (e.g. dexamethasone) were very beneficial to decrease NK/T cell in ECSIT V140A positive lymphoma (252). The immunomodulatory properties of thalidomide make it a suitable repurpose drug to use in COVD-19 patients, but it should not be used to treat female COVID-19 patients who are pregnant because of its teratogenic effects. There are two clinical trials regarding the utilize of thalidomide which is registered as NCT04273581 and NCT04273529.

5.8.9 Levamisole

One of the immune-modulator agents that act as an immune-stimulator in some conditions and immune-suppressor in other conditions depending on time and dose of administration, so it must be given with precautions (253). It works on cellular immunity especially T_h cell. It is proven that if it is administrated with ascorbic acid, it can reverse the T_h to normal level in the treatment of measles (254). For this reason, levamisole will be one of the candidate therapeutics to treat COVID-19 since lymphocytopenia is more common in this disease (255). It binds and deactivates papain-like protease (PLpr) which determines the virulence of SARS-CoV-1 (256). The bioinformatics proved that any drug that inhibits PLpr, it can inhibit also SARS-CoV-2 replication (257).

In concert, levamisole can boost the immune system to fight against the virus indirectly at one side; it may inhibit the SARS-CoV-2 replication via binding to PLpr at the other side. NCT04331470, NCT04383717, and NCT04360122 are the ongoing clinical trials to determine the efficacy of levamisole with other drugs to combat SARS-CoV-2 infection.

5.8.10 Cyclosporine A

This drug is mainly used in solid organ transplantation and some autoimmune diseases (258). It binds to cyclophilin A which is used as a receptor for nucleoprotein (NP) of SARS-CoV for virus assembly and release of a new virus (259). By this mechanism, it inhibits the spread of the virus from one cell to another and inhibits viral replication in SARS-CoV By inhibition of cyclophilin A (Figure 1B), it can mediate immune-suppressive property through the prevention of the formation of IL-2 (261). It can also act as an inhibitor of cyclophilin D, through this mechanism it protects mitochondria from damage by inhibition of MPTP pore and restoring unfolded protein response (81) (262, 263). It may beneficial for the treatment of COVID-19 (253, 264).

On the whole, cyclosporine A besides decreasing CS can rescue pneumocyte and cardiocyte from death via inhibition of MPTP pore and restoring UPR. We suggest strongly that utilization of this drug in the randomized preclinical trials to know its safety in COVID-19 patients since it has severe side effects when it is used in organ transplantation such as nephrotoxicity and bacterial infection. We also recommend low doses and in combination with antibiotics to overcome severe immunosuppressive properties and secondary bacterial infection that usually accompanies its usage. There are serious drug interactions between cyclosporine A and some antivirals (265). For this reason, we suggest not to use protease inhibitor antivirals such as lopinavir and ritonavir in clinical trials to overcome delay viral clearance as side effects of cyclosporine A. NCT04412758, NCT04392531, 2020-002123-11 (HIUS-4-2020) and 2020-001262-11 (FJD-COVID19-20-01) are identifiers for clinical trials that use cyclosporine A as symptomatic treatment of SARS-CoV-2 infection.

5.8.11 Melatonin

It is a hormone, secreted by the pineal gland in the brain, with anti-inflammatory, antioxidant, and immune regulator properties. Inflammation causes acute lung injury and ARDS in COVID-19 patients (255); the inflammation is the product of engaging of virus products to TLR4 that leads to IL-6 that has a central role in driving inflammation, melatonin prevents binding virus products to TLR4 thereby control inflammation (266) (Figure 1B). Inflammation enhances the production of oxidative stress that causes ALI; melatonin by decreasing free radical can control this damage (267) (Figure 1C). Because of these properties, melatonin can be regarded as a potential supportive care treatment in COVID-19 (266).

Melatonin has antiviral properties against some viruses such as the Ebola virus that reduce the severity of infection (268) but its effect on SARS-CoV-2 must be proved by the study. SARS-CoV-2 binds to ACE2 receptors on endothelium and cardiocyte causing cardiomyocyte damage, heart fibrosis, and endothelial dysfunction. Those cardiovascular complications caused by phosphorylation of STAT3 and JAK2 and increasing oxidative stress. It is believed that these abnormalities can be reversed by melatonin administration (269). We suggest using a high dose of melatonin especially to elderly patients who have poor prognostic factors to the COVID-19. It is inexpensive, safe, and easily available. Therefore, it must be used for prophylaxis or treatment of COVID-19 cases either alone or in combination with other treatments.

5.8.12 BP1-002

BP1-002 is a CTLA-4 inhibitor which is an immune checkpoint thereby it can activate T_h and CTL; the latter can kill the virus (Figure 1C). It also acts as an adjuvant so that it can be given with the vaccine for enhancing the production of B lymphocyte memory cells against future viral infection (270). It is manufactured by Beyondspring Company in the USA and it is previously used for the treatment of colorectal cancer (271).

This treatment may provide benefits for COVID-19 patients since the CTLA-4 inhibitor enhances the virus-killing ability of CTL. BP1-002 is not free form side effects because it can also drive T lymphocyte hyper-activation and exacerbate inflammatory mediated lung damage.

5.8.13 Brilacicin

Brilacicin is defensin like molecule, defensin, in turn, can acts as antiviral, blocks virus entry, and stimulates APC to the site of infection (272). It also binds to viral protein and thus prevents binding to their receptor in human cells. It is effective for blocking some virus including the influenza virus (273) but it is not tested on any CoVs, it may work by binding to spike protein of SARS-CoV2 (Table 1) (Figure 1B); it may also be used as an adjuvant with a vaccine for prophylaxis of COVID-19 but it beyond the scope of this review. However, the use of Brilacicin for the cure of COVID-19 is only a hypothesis as there are no clinical trials which prove an association of this drug with the disease.

5.8.14 Opaganib and RHB-107

Opaganib (Yeliva) and RHB-107 (upamostat) are selective sphingosine kinase (SK)-2 inhibitor and trypsin-like serine protease (S1 family) inhibitor respectively (34). Opaganib prevents the formation of SIP eventually it acts as an anti-inflammatory agent (Table 1) (Figure 1B). RHB-107 blocks the attachment of the virus to the cell consequently it works as an antiviral agent (274) (Figure 1B). They are used for many inflammatory-related conditions such as cancer and some gastrointestinal problems (275).

In most of the cases the lung damage in COVID-19 is not due to the virus but it is related to a hyper-inflammatory response to the virus; because of the anti-inflammatory properties of Opaganib and antiviral properties of RHB-107, COVID-19 patients may get benefit from them. However, the use of Brilacicin, Opaganib and RHB-107 for the cure of COVID-19 is only a hypothesis as there are no clinical trials which prove an association of these drugs with the disease.

5.8.15 Auranofin

It is a gold salt; it was approved by the FDA since 1985 for the treatment of RA. It has anti-inflammatory properties due to its ability to inhibit phosphorylation of JAK-1 and STAT-3 which act as signal transduction of IL-6 (276) and via inhibition of COX enzyme that mediates the formation of inflammatory prostaglandin (277) (Figure 1B). It has anti-cancer and antiviral activity because of the capability of increasing oxidative stress through inhibition of thioredoxin reductase, induction ER stress, and activation of UPR thereby it kills cancer cell and viral infect cell (278, 279). (280) proved in his study that auranofin is very effective in decreasing the viral load of SARS-CoV-2 in Huh7 tissue

culture cell by 70% and 85% after 24 and 48 hours auranofin treatment, respectively. They also uncovered in their study that inflammatory cytokines (IL-6, TNF-α, and IL-1β) and NF-KB would also decrease in tissue culture after 24 and 48 hours of auranofin treatment (Table 1).

Therefore, auranofin will provide "the light at the end of the tunnel" for treatment of ALI and inflammation in COVID-19 patients because it has anti-inflammatory, and antiviral properties.

5.8.16 Imatinib (Gleevec)

Imatinib, a TYK inhibitor of the JAK-TYK axis, is a medication based on inhibition of ABL kinase to the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal cancer. It affects cell migration by controlling actin polymerization. When translocation occurs between chromosome 9 and 22, ABL form chromosome 22 unites with BCR on chromosome forms BCR-ABL complex that has TYK activity leads to proliferation and migration of the cell in CML. Imatinib by blocking TYK activity is used for the treatment of this type of cancer (203) and eradication of CoVs since it also prevents the fusion of the envelope of the CoVs to the endosomal membrane (204). (205). The anti-coronal activity of Imanitib against MERS-CoV and SARS-CoV has been demonstrated. Imatinib has antiviral activity against coxsackievirus (206), vaccinia virus (207), and Ebola virus (208). One case report of COVID-19 patient was recorded to use imatinib (Table 1).

Conclusion

In conclusion, finding new vaccines and developing them to target the viruses is a hierarchic approach and also needs more time. However, it can be thought of as a backward approach by repurposing medications to control lung injury and commonly used immunotherapeutic drugs in controlling viral multiplication. If this approach is found to be convenient, then it can make a vast contribution to global viral security equity and global health. In this review, all the potential interventions for COVID□19 infection have been summarized according to previous immunotherapeutic treatments of SARS, MERS, and other diseases. It has been found that the immunotherapeutic treatments are very significant to regulate host immune response against RNA viral infection. It is also revealed that clinical trials that have launched to investigate potential immunotherapeutic treatments for COVID-19 are also highlighted.

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Declaration of interests

The author reports no conflicts of interest in this work.

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Table I. Selected targets and products being actively investigated for SARS-Cov-2

Immunotherapy	Mechanism	Number of patients	Proposed benefits or Results	References
NSAIDs (e.g. ibuprofen)	COX inhibitor	4	First, NSAIDs down-regulate ACE2 in the respiratory system that reduces pulmonary function. Second, NSAIDs up-regulate ACE2 especially in diabetic patients and patients that take ACE2 receptor inhibitors (such as losartan), the over-expression of ACE2 receptors might facilitate the entry of SARS-CoV-2 and increases the chance of infection. It showed worsening the symptoms of SARS-CoV-2 infection. This case has been shown in 4 children in France.	(104) (105) (281)
Corticosteroids **1-**	phosholipase A2 inhibitor		Methylprednisolone could improve both clinical and radiological outcome.	(118).

methylprednisolone)		46	Methyprednisolone suppresses the immune system by decreasing the production of anti-inflammatory and pro-inflammatory cytokines.	(282)
		101	Hindering of cytokine release syndrome in patients which is the main severe pathophysiology of COVID-19.	(283)
		56 from 85	Improves the outcomes as it has a great role in decreasing CRP level.	(284)
		18 from 34	MP has role is removing high fever, improving oxygenation, making breathing better and stops the progression of infection.	(285)
2- dexamethasone			the use of dexamethasone as supportive care for moderate and	(119)

		350	severe COVID-19 patients lead to decrease duration of mechanical ventilator and mortality rate It decreases organ failure problems in the patients after careful usage.	(286)
Tocilizumab (TCZ	IL-6 inhibitor	21	It caused improvement of both the fever and oxygenation (75%) in COVID-19 patients. Apart from that, both the biochemical profile (peripheral lymphocytes 52%) and radiological opacifications (90.5%) are improved.	(136)
		15	It decreases cytokine storm such as IL-6 storm. It is very effective in critically ill patients. It is regarded as antagonist for IL-6	(287)

		1 100	receptor that decreases mortality rate. Tocilizumab treated a man 60 years old patient of COVID-19 case with multiple myeloma. It has role in returning CRP, Ferritin and Fibrinogen to normal level	(288) (289)
Sarilumab	IL-6 inhibitor	8 of 15 patients	Improvement in oxygenation with decreasing in the inflammatory response.	(290)
Siltuximab	IL-6 inhibitor	21 33 of 188	Siltuximab in 700-1200 mg resulted in improvement of clinical conditions in 33% patients through reduction of CRP, worsening the condition in 24% of patients, and there were no change in the clinical conditions of the others. It decreased the mortality rate in a significant way in the patients who	(138) (291)

			took Siltuximab. As it has role in lowering the hyperinflammation associated cytokines.	
Leronlimab	chemokine receptor 5 (CCR5) antagonism	11	It decreases the viral load, IL-6 and CCL5. There is no space on CCR5 on macrophage to be occupied by CCL5.	(292)
Bevacizumab	VEGF antagonism			
Adalimumab	Anti-TNF-α., may decrease adhesion molecule and migration of leukocyte	1 2	It is used in a 30 year male with Crohn's disease with COVID-19, in which fever and chest pain have been disappeared after 24 hours. After 5 days, he was asymptomatic. It has role in quick recovery from COVID-19 symptoms. Even in the patients with psoriasis.	(293) (294)
Emapalumab	IFN-γ antagonistic property.			

Anakinra	Inhibitor of inflammasome and IL-1β	29 9 (-1) 52 anakinra group with 44 without anakinra	1-High dose of it resulted in decreasing CRP and improving of respiratory function in 72% of patients, the rate of survival among patients were 90%. 2- Moderate dose of it brought about decrease in CRP in 5 patients out of 8 patients at day 11, stopping in extra pulmonary lesion at day 8. the rate of survival among patients were 100% 3-it decreased the use of mechanical ventilation among anakinra group and the death rate without producing any serious side effects	(295) (296) (297)

		8	It decreased the need for vasopressors, lowered HScore, and improved respiratory function in those sever patients.	(298)
		11 of 14	It decreased MV, patients discharged home soon.	(299)
		5	After using of high dose of it, it showed very rapid improvement in respiration with a very fast clearance of inflammation.	(300)
		1	A 33-year old man with pericarditis has been treated after infected with COVID-19 by using IL-1 antagonist (anakinra)	(301)
Eculizumab	Inhibitor of complement factor C5 and prevents MAC formation.	4	Eculizumab induced a drop in inflammatory markers. Mean C Reactive Protein levels dropped from 14.6 mg/dl to 3.5	(302)

		1 out of 4	mg/dl and the mean duration of the disease was 12.8 days. Prevent patients to increase CRP, LDH, hospitalization, not need oxygen supploementation	(303)
Ravulizumab (Ultomiris)	Inhibitor of complement factor C5 and prevents MAC formation.	1 out of 4	Prevent patients to increase CRP, LDH, hospitlaization	(303)
IFX-1	Inhibits the biological activity of C5a			
AMY-101	Inhibitors of C3	1	Normalalization of CRP, LDH; decrease oxygen requirement and improvement of leukocytosis and lymphocytopenia	(304)
Nivolumab	Inhibitors of PD-1			
Interferon	Decreases the SARS-CoV-2 activity through the	77	1-Vero E6 cell showed decrease in viral titer after 24	(305)

	phosphorylation of STAT1	20	and 48 hours of IFN-α treatment by 3 logs and 4 logs, respectively. 2- It is effective for reducing viral load and inflammatory markers (CRP and IL-6).	(179)
		5	Fever decreased in all patients just in 7 days, all other symptoms are declined gradually, and viral load deceased to zero after 10 days.	(306)
		20	Oxygen demand and symptoms are improved, with the decreased of hospitalization period.	(307)
		2944	All patients were feeling good, fever has been decreased, and there is no any death report after discharge.	(308)

		42	Interferon alpha nasal drops showed an protective effect for most susceptible people.	(309)
		60	Mortality rate decreased significantly, and discharging has been increased.	(310)
		50	Improvement in oxygenation and increasing the discharge from hospital. Decreasing in the viral load.	(311)
		814	Higher recovery rate in those who received IFN-alpha 2b.	(312)

Convalescent plasma	Eradicates the virus through inhibition of viral attachment and replication.	6	All patients did not admit to ICU. Some patients showed clearance of virus for throat swab while some others showed improvement in radiological examination.	(313)
		10	Improvement in the symptoms in severe cases.	(314)
		5	Viral load decreased, fever decreased within 3 days after transfusion, oxygen level increased.	(315)
		4	All patients recovered from the infection including one pregnant woman. This	(316)

			method has role in boosting the immune system of newly infected patients.	
		2	Increasing in the survival rate of sever cased patients, in which both patients present sever pneumonia and ARDS. This method doesn't have any adverse effect.	(317)
		6	Decreasing in the symptoms, radiological improvements and elimination of virus without any adverse effect.	(313)
		80	Great improvement has been seen in patient's symptoms who received the convalescent plasma before day 14.	(318)

		6	COVID-19 Negative results achieved after 3 days of infusioin.	(319)
		7	Neutralization of viremia after CP transfusion.	(320)
		6	Not requirement for mechanical ventilation. Early discharge from hospital.	(321)
		4	It's regarded as a potential therapy for severe cases without any adverse effect.	(322)
		52 of 103	Decrease in the severity of the disease, faster discharge.	(323)
		25	It is regarded as a safe method for treating this disease. 9 of the patients cured just after one week.	(324)

Baricitinib	JAK and AAK inhibitors	20 out of 76 (56 are control)	It inhibits endocytosis of virus and inflammation mediated SARS-CoV-2 infection Reduce mortrality rate (5%), reduce oxygen need, and CRP while increase P/F ratio	(190) (325)
		1 out of 4	Her IFN-γ, TNF-α and IL are lower than the others	(326)
		12 and 12 standard control	Symptoms, CRP, procalcitonin spO2 and PaO2/Fi O2 are improved	(327)
		15	Most of the pateints showed improvement in presenting	(328)

			symptoms, inflammatory markers, and oxgen requirement	
		22	Supplemental oxygen requirement, ferittin and CRP levels are reduced in most of the patients.	(329)
		113 patients and 78 controls	Fatality rate is decreasesd, most of the clinical, laboratory (IL-6 and CRP) and respiratory functions are improved.	(330)
Ruxolitinib	Inhibitor of JAK, and activate Treg	14	It reduces (COVID-19 inflammation score) by ¾ in most of patients.	(331)
		20 out of 41	Improved in CT of lung.reduced mortrality rate.	(332)

		1	Levele of 7 cytokines (IL-6, NGF-β, MIP-α, MIP-β, VEGF, IL-12 (P40) and macrophage migration inhibitory factors and CRP were decreased IL-6, CRP decreased while IL-2R increased.	(333)
Tofacitinib	Inhibitor of JAK1 and JAK3			
Jaktinib	JAK1 and JAK2 inhibitor			
Imatinib	TYK inhibitor	1 (Case report)	Pulmonary opacities were disappeared. Her clinical signs improved.	(334)
Thymosin	Activates different subsets of T-cells (CTL, Th, and Treg) and NK cell activity, and reverses the side effects of corticosteroids	76 severe cases In vitro 11 out of 25	It increased survival rate by restoration of lymphocytopenia and reversion of exhausted T cell. It also normalized the CD+4/ CD+8 ratio. It increased number of T cells. It did not change CD+4/	(190)

			CD+8 ratio, it protect T cell from excessive activation. It decreased granzyme B. Number of lymphocytes were raised in critical patients after treatment	(136)
Fingolimod	S1PR inhibitor			
Pirfenidone	Targets IL-1β, IL-4 and anti-oxidant effect and reduce pulmonary fibrosis in post SARS-CoV-2 infection			
CD24FC	Prevents the formation of NF-KB and reduces IL-6 and IL-1			
Tranilast	Inflammasome inhibitor blocks the formation of inflammatory prostaglandins via inhibiting COX2 in fibroblast and macrophage and decreases the release of IL-6 from endothelial cells.			
IL-2	Anti-inflammatory and anti-viral properties			

Rhu-GM-CSF (sargramostim)	Act as an immune-modulator that activate alveolar macrophage to remove debris			
vMIP	Strong chemokine antagonism	*In vitro*	It increased CTL, inhibited chemokine receptor and related signal pathway	(335)
NK cell	Anti-viral property			
T cell immunotherapy	Reverses T-cell deficiency			
Pluristem (PLX)	Anti-inflammatory characteristics, and activate Treg and M2 macrophages	7 (only 6 patients completed 1 week of treatments)	The survival rates were 100% among Israeli patients. 66% of patients were showing improvement of respiratory parameters.	(336)
Thalidomide	Immunomodulatory properties	1 (case report)	It decreased cytokines including IL-6, IL-10, and IFN-γ. It raised the absolute lymphocyte count.	(337)
Levamisole	Reverse the Th to normal level to treat lymphocytopenia, and decreases inflammation			
Cyclosporine A	Cyclophilin A, MPTP pore and D inhibitors			

Melatonin	Prevents binding virus products to TLR4, and ameliorates free radical driven lung damage			
BPI-002	CTLA-4 inhibitor			
Brilacidin	Antiviral property that bind to spike protein of SARS-CoV-2			
Opaganib (Yeliva: ABC294640)	Sphingosine kinase (SK) inhibitor	7 (2 patients were excluded)	It decreased the level of CRP (non-significantly) but it increased the level of lymphocytes.	(338)
RHB-107 (Upomastat, WX-671)	Trypsin-like serine protease (S1 family) inhibitor			
Auranofin	Inhibits phosphorylation of JAK-1 and STAT-3, and inhibits COX		Inflammatory cytokines (IL-6, TNF-α and IL-1β) and NF-KB would also decreased in tissue culture after 24 and 48 hours of auranofin treatment. It is very effective in decrease viral load of SARS-CoV-2 in Huh7 tissue culture cell by 70% after 24 hours of auranofin treatment and 85% after 48 auranofin	(280)

			treatment	

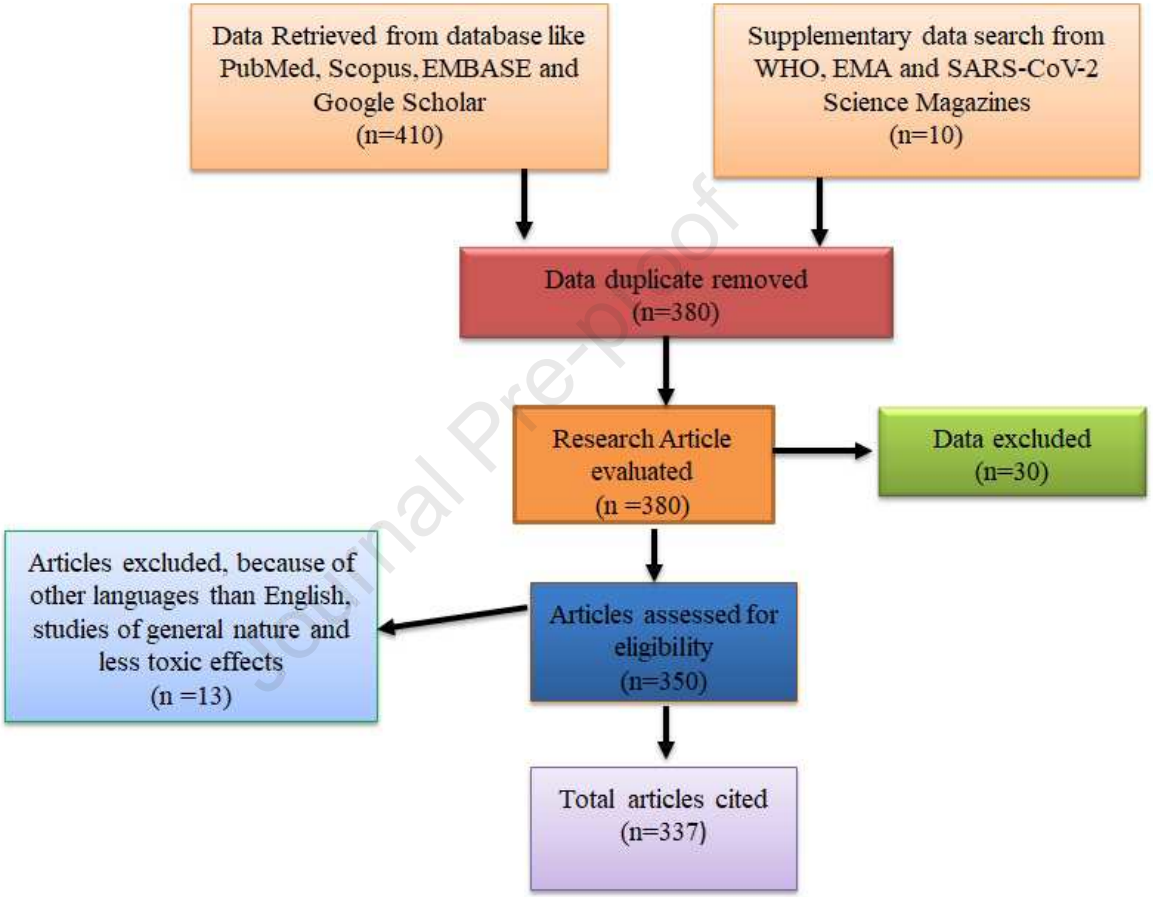
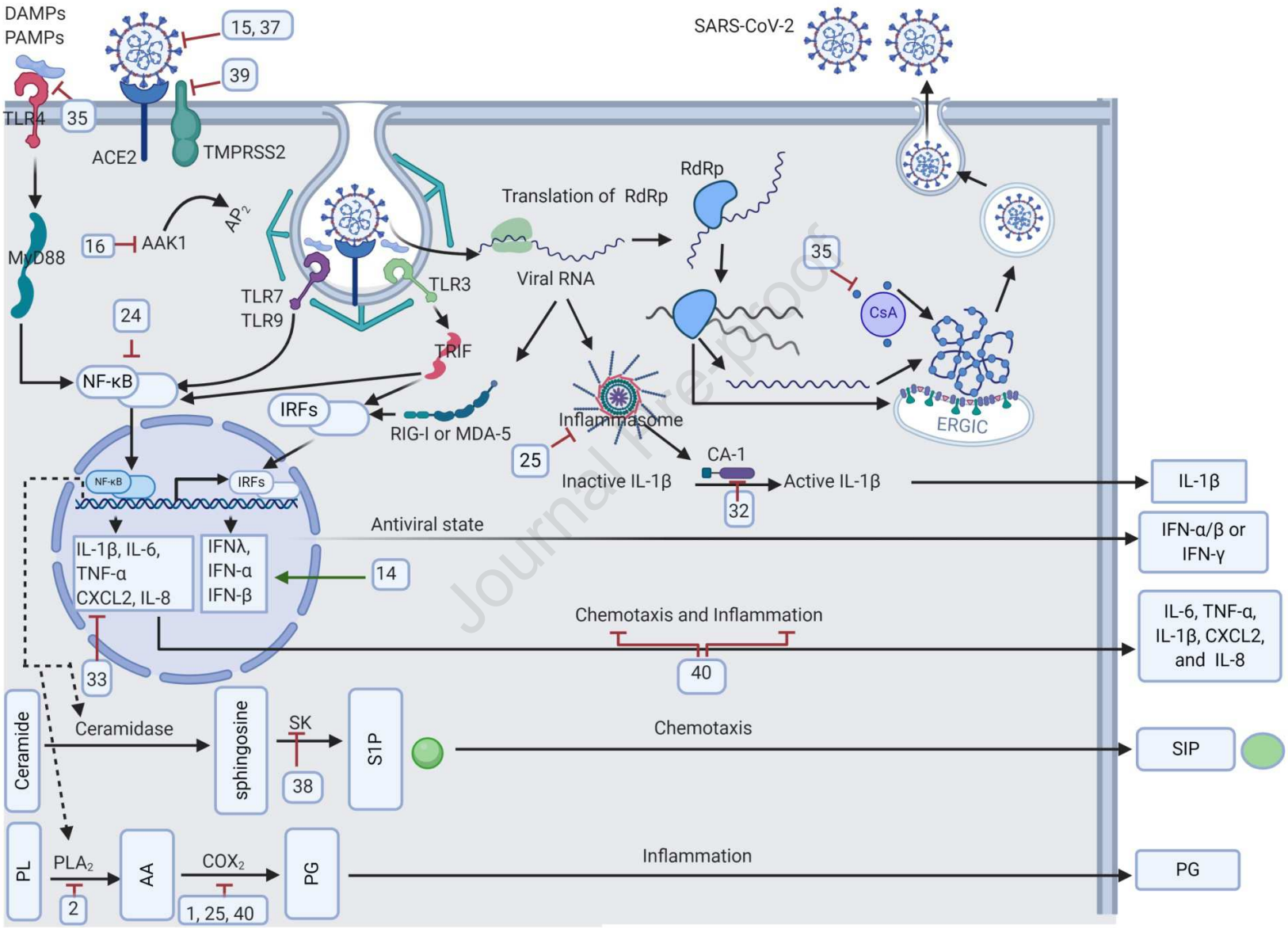


Figure 1A: Flow diaghram of included studies. The flow chart depicts the number of citation and resources materials that have been screened, excluded and/or included in the review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PAMPs
TLR4
35
15, 37
39
ACE2
TMPRSS2
SARS-CoV-2
MyD88
16
AAK1
AP2
TLR7
TLR9
TLR3
Translation of RdRp
RdRp
Viral RNA
35
CsA
24
TRIF
NF-κB
IRFs
RIG-I or MDA-5
Inflammasome
25
CA-1
Inactive IL-1β
Active IL-1β
32
ERGIC
IL-1β
Antiviral state
IL-1β, IL-6,
TNF-α
CXCL2, IL-8
IFNλ,
IFN-α
IFN-β
14
IFN-α/β or
IFN-γ
Chemotaxis and Inflammation
40
IL-6, TNF-α,
IL-1β, CXCL2,
and IL-8
33
Ceramide
Ceramidase
sphingosine
SK
38
S1P
Chemotaxis
SIP
PL
PLA2
2
AA
COX2
1, 25, 40
PG
Inflammation
PG

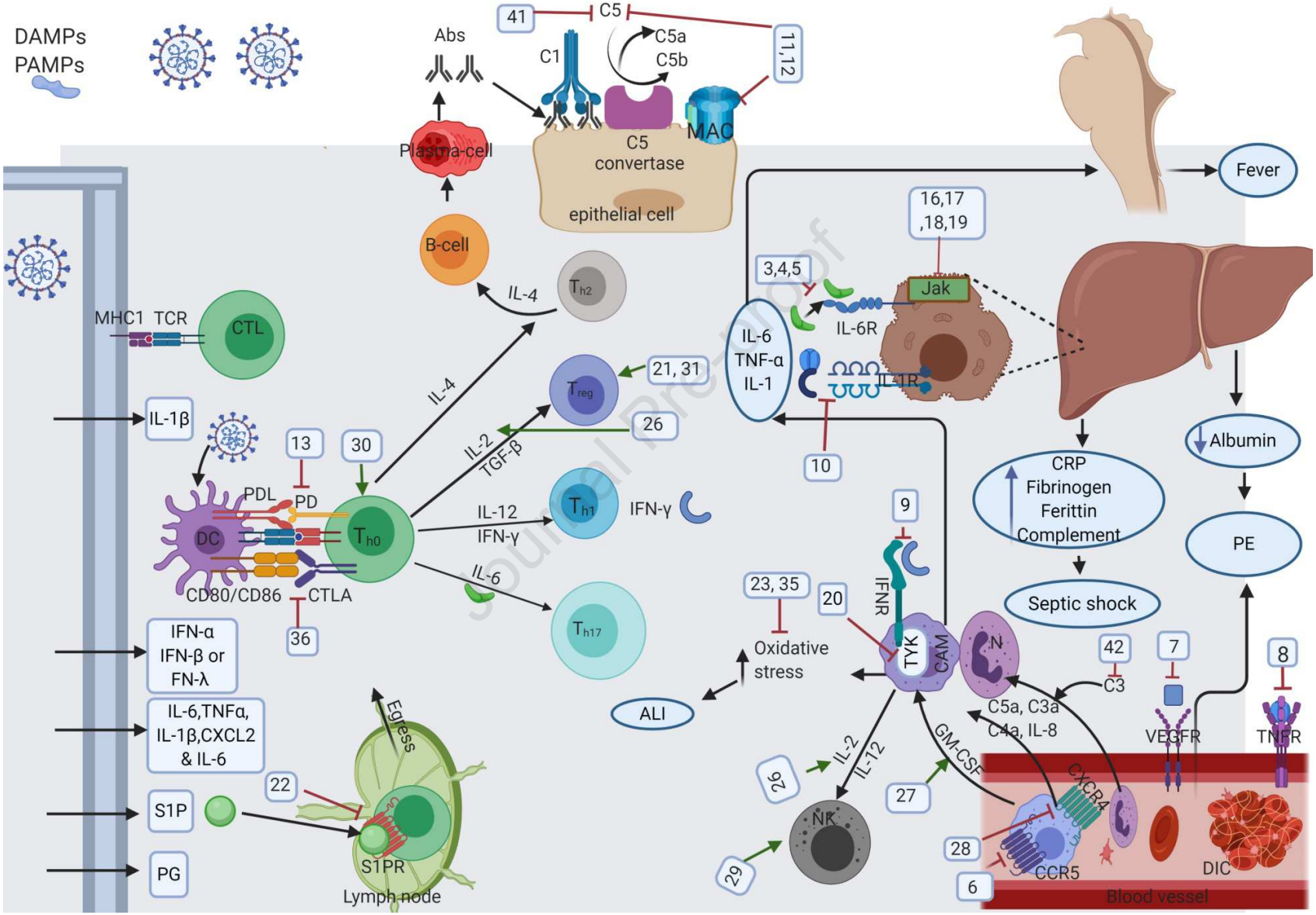
Figure 1B: Immune response, immunopathology, and mechanism of action of immunotherapeutics for SARS-CoV-2 infection (intracellular). Inhibitory effects represented by red lines, while activating effects represented by green lines. Created with BioRender.com

The spike protein surrounding SARS-CoV-2 engages in angiotensin-converting enzyme 2 (ACE2) and permits virus entry. Inhibitors like brilacicin (37) and antibodies in the convalescent plasma (15) prevent the binding of the virus to its receptor. TMPRSS2 may help the virus to enter the cell which can be inhibited by RHB-107 (39) therapy. After binding of the virus to its receptor, it enters the endosome. It needs AAK1 for endocytosis as a regulator (it is inhibited Baricitinib (16)). After membrane fusion with the endosomal membrane, it releases naked RNA into the cytosol. Inside the cytoplasm, it translates its RNA-dependent RNA polymerase (RdRp) to replicate its RNA and it undertakes gene expression. After the synthesis of protein and viral RNA, they accumulate inside the ER and Golgi apparatus. they leave ERGIC by exocytosis. it needs cyclophilin A to virion assembly which may be inhibited by Cyclosporine A (34). Consequently, the new virions are formed and released to infect another cell.

The endocytosis of the virus is initiated by the engagement of SARS-CoV-2 and ACE2 on the surface of the infected cell through S protein and TMPRSS2. The virus releases its genome into the cytosol. Naked RNA is recognized by cytosolic receptors such as RIG-1, MDA-5, or NLRP3. RIG-1 and MDA-5 activate IRFs that enter the nucleus. Once NLRP3 activated by naked RNA, eventually it causes activation of inflammasome which in turn leads to activation of caspase-1 (CA-1), inflammasome is inhibited by tranilast (25) while CA-1 is inhibited by thalidomide (32). CA-1 drives the activation of IL-1B which is a potent inflammatory cytokine. When dsRNA is formed during RNA replication of the virus, the immune response is elicited by activation of TLR-3 within the endosome, IRF, and NF-Kb which results in the production of inflammatory cytokines and interferons (IFNs). IFNs generation has an essential role in releasing antiviral proteins to defend healthy cells and it is augmented by interferon therapies (14). TLR□4 on the cell membrane surface might recognize PAMP and DAMP of the virus and stimulate proinflammatory cytokines via the MyD88□ dependent signaling pathway and NF□κB activation. Melatonin (35) is believed to prevent these interactions while NF□κB is inactivated by CD24FC (24) treatment. TLR7/TLR9 is activated upon sensing PAMP of SRAS-CoV-2 (i.e ssRNA), similar to the

TLR4 signaling system, it can activate the MyD88□dependent signaling pathway and NF□κB. The other transcriptional activations of NF□κB beside inflammatory cytokines and chemokines are ceramidase and phospholipase A2 (PLA2) enzymes. The former catalyzes ceramide in the cell membrane into sphingosine which further catabolized by shingokinase (SK) into chemotactic sphingosine 1 phosphate (S1P). Inhibitors like Opaganib (38) can inhibit the SK enzyme, it prevents the formation of S1P that egresses the T lymphocyte from the lymph node to the site of inflammation. Regarding PLA2, it degrades phospholipid (PL) in the cell membrane to form arachidonic acid (AA) that in turn catabolized by cyclo-oxygenase 2 (COX2) enzyme into inflammatory prostaglandin (PG). PLA2 is inhibited by corticosteroids (2) and while and COX2 is inhibited by NSAIDs (1) and auranofin (40).

Interactions of the virus to the cell results in the generation large amount of cytokines (TNF-α, IL-1, IL-6) and chemokines (IL-8 and CXCL2) from the infected cell. The former is inhibited by levamisole (33) to mitigate cytokine storm (CS) and acute lung injury that may occur in COVID-19 patients. While the chemokines recruit the lymphocyte and leukocyte to the site of inflammation.


DAMPs
PAMPs
Abs
41
C5
C1
C5a
C5b
11,12
MAC
C5
convertase
epithelial cell
Plasma-cell
B-cell
IL-4
Th2
Fever
16,17
,18,19
3,4,5
Jak
IL-6R
IL-6
TNF-α
IL-1
IL-1R
MHC1 TCR
CTL
IL-1β
IL-4
Treg
21, 31
IL-2
TGF-β
26
13
30
PDL
PD
DC
Th0
IL-12
IFN-γ
Th1
IFN-γ
IL-6
Th17
CD80/CD86
CTLA
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Albumin
CRP
Fibrinogen
Ferittin
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IFNR
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TYK
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C3
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8
VEGFR
TNFR
C5a, C3a
C4a, IL-8
IFN-α
IFN-β or
FN-λ
IL-6,TNFα,
IL-1β,CXCL2
& IL-6
S1P
PG
22
Egress
S1PR
Lymph node
ALI
IL-2
IL-12
26
NK
29
27
GM-CSF
CXCR4
28
CCR5
6
DIC
Blood vessel

Figure 1C: Immune response, immunopathology, and mechanism of action of immunotherapeutics for SARS-CoV-2 infection (extracellular). Inhibitory effects represented by red lines, while activating effects represented by green lines. Created with BioRender.com

The dendritic cells (DCs), The professional antigen-presenting cells, present viral protein to Th cell then different subsets of Th (Th1, Th2, Treg, Th17) is polarized depending on the cytokines. COVID-19 Patients had elevated levels of IL1B, IFN-γ, IP10, and MCP-1 signifying hyper-activation of Th1 cell reactions. The activated T cells egress from the lymph node to the site of infection through the interaction of S1P to S1PR which can be blocked by Fingolimod (22).

IFN-γ causes activation of macrophage through binding to its receptor on it; tyrosine kinase (TYK) is the signal transduction of IFNR. Macrophage activation can be inhibited by prevent binding IFN-γ to its receptor by emapalumab (9) or blocking TYK via imatinib (20).

When Th2 is polarized, different types of cytokine (IL4, IL5, IL10, and IL-13) will be generated, primarily help B cells to produce antibodies which in turn trigger classical activation of complement 3 (C3) and (C5) which culminate in membrane attack complex (MAC) formation and damage of the viral infected cell. C3 is inhibited by AMY-101 (42). C5 and MAC are inhibited by eculizumab (11) and ravulizumab (12). C3a, C4a, and C5a are also formed which act as anaphylatoxin that attracts neutrophil and macrophage to the site of inflammation and increases oxidative stress that induces acute lung damage (ALI). The oxidative stress is mitigated by the administration of pirfenidone (23) and tranilast (25) and also by the administration of C5a antagonists such as IFX-1 (41). Neutrophil and Monocyte (macrophage) are synthesized and attracted to the site of inflammation by GM-CSF which is augmented by GM-CSF (27). Another factor to prevent migration of monocyte from the bloodstream to the site of infection is to block its chemokine receptors such as CCR5 and CXCR4 by leronlimab (6) and vMIP (28), respectively.

The production of the polarized Th17 cells during SARS-CoV-2 infection has been associated with elevated levels of IL-6 and could also be influenced by transforming growth factor-β (TGFβ). Th17 cells are associated with driving harmful inflammation in the case

of SARS-CoV-2 infection. The IL-17 is released by Th17 acting as a chemotactic protein that drives monocyte and neutrophil to the site of infection.

TGF-β and IL-2 play a vital role in the production of induced Treg cells; Treg can mitigate hyper-inflammatory response once activated. Treg can be supported by the administration of IL-2 (26), thymosin (21), or pluristem (31) therapy. SARS-CoV-2 is eliminated directly by the activation of CTL and NK cells. Both of them are influenced by IL-2 which secretes by naïve T helper cell (Th0) which in turn augmented by T-cell immunotherapy (30). CTL and NK cells are boosted by the administration of IL-2 (26) therapy. Once the SARS-CoV-2 virus is introduced into the tissue cells, such as respiratory epithelial cells, viral peptides are presented via class I major histocompatibility complex (MHC) proteins to CTL.

Inflammatory cytokines (IL-6, IL-1, and TNF-α), that secrete by activated DCs and viral infected cells, have an essential role in acute phase response and cytokine storm (CS) during SARS-CoV-2 infection. They affect on brain stem to produce fever. They induce the liver to produce acute phase reactants (CRP, ferritin, and fibrinogen). The latter two contribute to coagulopathy and septic shock.

We can depress the action of IL-6 either by preventing its binding to its receptor (through tocilizumab (3), sarilumab (4) or siltuximab (5) treatments or inhibiting its signal transduction system by Janus kinase (JAK) inhibitors such as baricitinib (16), ruxolitinib (17), tofacitinib (18) or jakotinib (19). TNF-α besides its role in the acute-phase response can bind to its receptor on the blood vessel to increase adhesion molecules and enhances the extravasation of neutrophil that causes ALI. It also works with VEGF to induce pulmonary edema by disrupting the endothelial barrier of lung blood vessels. TNF-α and VEGF are inhibited by preventing binding to their receptor by adalimumab (8) and bevacizumab (7), respectively. Regarding IL-1, it can be inhibited by preventing its ligation to the receptor by Kineret (10).

Lymphocyte exhaustion and lymphopenia are common in SARS-CoV-2 infection which can be reversed by the administration of programmed cell death- protein1 (PD1/PD-L1) inhibitors nivolumab (13), or cytotoxic T-cell-associated protein 4 (CTLA4) inhibitors BP1-002 (36) could have an important role in the prevention of lymphopenia or restore lymphocyte counts in severe cases of COVID-19 patients.

Highlights

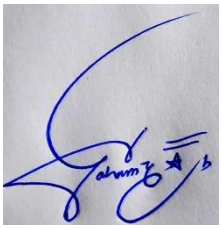
- Effective and novel therapies against COVID-19 are urgently needed.
- SARS-CoV-2 invade the immune and nervous system.
- Cytokines could be promising therapeutic target for the SARS-CoV-2 severe cases therapy.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NO competing interests.



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