COVID-19, T Cells, Cytokines and Immunotherapy: Review

Nesrin I. Tarbiah[1*]

[1]*Biochemistry Department, King Abdulaziz University, Jeddah, Saudi Arabia.*

ABSTRACT

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus (COVID-19), materialized in the city of Wuhan and quickly spread to form a global pandemic. An essential role in the immune system is undertaken by lymphocytes, which defend against bacteria, viruses, fungi, and parasites. Previous study found that very severe COVID-19 patients had suppression of the immune response enabling the virus to spread and cause more damage. This was evident by the changes in their white blood cell and lymphocyte count. Early clinical findings suggest that those suffering from severe COVID-19 have reduced numbers of lymphocytes, monocytes, and other granulocytes. One of the most efficient responses for a variety of viral infections is cellular immune response activation, especially via T cells. Viruses can be eliminated by T cytotoxic (CD8+) (Tc) in the host body, these secrete a variety of molecules, including interferons (IFNs), granzyme, and perforin. T helper (CD4+) (Th) cells help by assisting cytotoxic T cells and B cells to eliminate viral infection. CD8+ and CD4+ work together in a coordinated immune response with other constituents to primarily resolve acute viral infections, and after to produce protection against any reinfection.
Also, COVID-19 causes dramatic changes in cytokine profiles and serological markers. Therefore, the subsets of immune cells and the level of the pro-inflammatory cytokines are crucial evidence to

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Corresponding author: E-mail: ntarabah@kau.edu.sa;

determine the severity of COVID-19. The disease severity has already been proved to be associated with the disruption in the proinflammatory chemokine response, this eventually leads to a cytokine storm and progression of cytokines release syndrome (CRS). This review aimed to demonstrate a full understanding of the alterations to the immune response by determining the T-cell expression and cytokine levels against the pathological processes of COVID-19, which can be a significant step in early treatment and diagnosis of this disease, in reduction of COVID-19 mortality cases, and to emphasize the most recent and current studies to try to identify new immuno-therapeutics for COVID-19.

Keywords: Covid-19; cytokines release syndrome; immunotherapies; T-cells.

1. INTRODUCTION

The end of 2019 witnessed the discovery of a unique coronavirus in Wuhan city, Hubei province, in the Republic of China. This virus soon turned into a global pandemic that affected almost all countries in the world and impacted all aspects of life. This is a novel virus known as COVID-19 and belongs to the coronavirus family [1,2]. The virus mainly causes acute respiratory tract infections.

The name "coronavirus" comes from the crown-like appearance of spike glycoproteins on the envelope. The virus particle consists of a single-stranded RNA (26 to 32 kilobases in length) encircled by a structural protein shell [3]. The genetic material of the virus encodes the four essential structural proteins (membrane, spikes, envelope and nucleocapsid) [4]. Coronaviruses are zoonotic viruses that are classified into one of four different genera: gamma, delta, beta, and alpha [5]. Few coronaviruses have been successful in achieving the cross-species jump and becoming pathogenic to humans; this has been seen in a few outbreaks that have caused significant fatalities during the last 20 years, such as Middle East Respiratory Syndrome Coronavirus (MERS CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [6,7].

The current 2019 coronavirus (COVID-19) was isolated from human respiratory epithelial cells and is the result of the virus SARS-CoV-2. The particle size of the virus is around 140nm. It belongs to the beta group, and it has a different genetic material when compared to the SARS-CoV and MERS CoV seen previously [8]. The pathogenesis of COVID-19 is initiated by the binding of the virus to the pulmonary epithelial cells. This triggers a chain reaction starting with the immune system, causing an increase in inflammatory mediators such as Interleukin-6 (IL-6). This widespread inflammatory reaction is also responsible for increasing vascular leakage. The fluid and cells move into the alveolar cavity and eventually cause a severe interruption of respiration by causing shortness of breath and pulmonary dysfunction [9]. COVID-19 symptoms begin to appear after an incubation period of up to 10 days, and the clinical symptoms commonly include cough, fever, nasal congestion, sore throat, joint pain and exhaustion. In more severe cases, many suffer from dyspnea, shortness of breath, pneumonia, and hypoxemia. This may escalate to septic shock, extreme respiratory distress syndrome, coagulation dysfunction, metabolic acidosis, and systemic organ failure, especially in the kidney, liver, and heart [6,10,11].

Several studies have reported elevated inflammatory cytokine levels and severe pulmonary damage in MERS-CoV and SARS-CoV infections, and this has recently been shown in COVID-19 as well [6,12]. Also, one research has found that patients with COVID-19 have elevated liver lactate dehydrogenase (LDH), C-reactive protein, and erythrocyte sedimentation rate (ESR) levels [7]. Another important observation in severe COVID-19 cases is presence of metabolic acidosis due to elevated levels of lactic acid in the blood, which may be responsible for the inhibition of lymphocyte diffusion [13].

2. METHOD

The data presented in this literature review were retrieved using PubMed., ScienceDirect and Google Scholar. Only article in English were included.

3. COVID-19 RECEPTORS

On the coronavirus viral envelope, there is a spike glycoprotein that binds to specific receptors on host cell membranes. Previous investigations have found angiotensin-converting enzyme 2

(ACE2) is a functional, specific receptor for SARS-CoV-2 [14,15]. The study by [16] reported SARS-CoV-2 could enter cells expressing ACE2 cells, but not those lacking ACE2 or those that expressed other coronavirus receptors, including aminopeptidase N and dipeptidyl peptidase 4 (DPP4), which confirms the importance of ACE2 as it is the SARS-CoV-2 cell receptor [14,16]. Other studies have shown that SARS-CoV-2 spike glycoprotein binding affinity for ACE2 can be 10- to 20-fold stronger than the binding between ACE2 and SARS-CoV [14,17]. Nearly all human organs express ACE2 in differing degrees; for example, immunohistochemical methods and single-cell RNA-seq analysis have shown the respiratory system mainly expresses ACE2 on type II alveolar epithelial cells, and it is more weakly expressed on the nasopharynx, nasal and oral mucosa epithelial cell surfaces, implying the primary SARS-CoV-2 target are the lungs [14,18,19]. ACE2 is also expressed highly on bladder urothelial cells, proximal tubule cells of the kidney, and myocardial cells, and it is expressed plentifully on small intestine enterocytes, especially within the ileum [18,19] (Hui Zhang et al., 2020). Macrophage phagocytosis-associated and cell free virus can migrate to other high ACE2 expression organs from the lungs via blood circulation. For example, for SARS patients who developed diarrhea, up to 67% of them had enteric symptoms, which has also been seen in number of COVID-19 patients [14,20,21,22]. Within small intestine enterocytes, active viral replication has been shown and there have been successful isolations of SARS-CoV-2 in fecal specimens [14,23,24].

As well as acting as the SARS-CoV-2 and SARS-CoV receptor, ACE2 can hydrolyze Ang-II to angiotensin-(1–7), and formation of ACE2/angiotensin-(1–7)/MAS can neutralize the RAS negative effects and causes anti-inflammatory responses [14] (Rodrigues Prestes, Rocha, Miranda, Teixeira, & Simoes-e-Silva, 2017). Different studies have reported infection of SARS-CoV downregulates expression of ACE2 on cells, which disrupts the Ang-II/angiotensin-(1–7) and ACE/ACE2 physiological balance, and that can result in severe injury to organs [14] [25]. This is supported by the fact that SARS-CoV-2 is a variant of the SARS-related coronaviruses and it also uses the ACE2 receptor, so ACE2 downregulation can be involved in COVID-19 multiple organ injury, and most COVID-19 critically ill patients had damage to multiple organs, such as cardiac injury, pneumothorax, acute lung injury, liver dysfunction, and acute kidney injury [14,26] .

4. SARS-CoV-2 And T-Cells

There is a direct impact of COVID-19 on the lymphocytes mediated by the coronavirus ACE2 receptors, which are expressed by the lymphocytes. They render these cells a direct target of the virus and viral infection can affect the lymphatic organs, such as the spleen and thymus gland [13]. In viral clearance, T cells have a vital role, as CD8+ T cells secrete a range of molecules, including IFN-γ, perforin, and granzymes, which help to remove the viruses [27,28,29]. CD4+ Th cells, at the same time, assist B cells and Cytotoxic T cells (Tc) to increase their pathogen clearance ability [30]. However, T cell exhaustion can be caused by persistent virus stimulation, leading to reduced function and loss of cytokine production [31,27]. One study reported that the CD8+ and CD4+ T cell counts were lowered in the samples of peripheral blood of COVID-19 patients; those cells were found to be hyper-activated and contain a high concentration of cytotoxic granules, which could mediate the cytokines release syndrome (CRS) [13]. The fall in the T cell numbers is most likely due to the extreme inflammation caused by SARS-CoV-2. Another study showed that, compared to healthy individuals COVID-19 patients did not show any significant differences for the ratio of CD4+: CD8+, but CD8+ expression levels were significantly higher in patients with COVID-19 compared to healthy individuals. This suggests infection of COVID-19 triggers the cellular immune response, which is then enacted via hyperactivation of Tc lymphocytes and overexpression of CD8+ [32].

Within the normal immune system, the ratio of CD4+ to CD8+ is usually around 2:1. Human immune response research, has shown that, in some viral infections, the CD4:CD8 ratio can be inverted and disrupted to become <1:1 [33]. COVID-19 studies have shown that the CD4:CD8 ratio in patients was 2:1, which is the same as the normal value, indicating there was no significant difference when the results were compared with those for the healthy group of controls [32,34]. There was a significant increase in the CD8+ median fluorescence intensity (MFI) when comparing the COVID-19 group with healthy individuals, but this was not observed for CD4+ MFI, as there were no significant differences for the patients with COVID-19 and

the healthy control group. A normal CD4:CD8 ratio combined with a significant CD8+ MFI increase shows how the immune response of a person after infection with COVID-19 works by providing a normal CD4:CD8 ratio with increased levels of expression for CD8+ cell markers. CD8+ is important during T cell activity, as increased cytotoxic activity by T lymphocytes can be mediated by increased expression of CD8+ and hyper-activation of Tc antiviral responses [32].

Some chronic viral diseases, including AIDS, produce decreased CD8+ levels; the difference with COVID-19 patients could be attributed to the shorter infection duration when compared with the chronic, long duration of infections like AIDS [32,35].

Other research has shown that in COVID-19 patients lymphocyte numbers in the peripheral blood were reduced significantly [27,12,21,13,36]. One study indicated that SARS-CoV-2 patients have lower B-cell, Th cell, T suppressor and natural killer (NK) counts. Subsequently, cytokines stormed, and inflammatory cytokines increased, leading to the occurrence of the subsequent immune response mechanisms. Also, in severe COVID-19 patients, the concentration of white blood cells and the ratio of neutrophil lymphopenia (NLR) increased, while monocyte, eosinophils, and basophils decreased. Given the pivotal role of lymphocytes in modulating the immune response, it would be interesting to investigate the NLR and lymphocyte subsets. This would help in the initial diagnosis and treatment of COVID-19 and in screening for serious infection, leading to the development of improved therapeutic strategies to counteract detrimental pathological responses [37].

Another COVID-19 outcome includes a rise in the native Th cells with a concomitant reduction in the mature Th and suppressor cells, which could be due to the deficiency in the regulatory T cells. As the increased NLR in severe COVID-19 patients suggests these neutrophils could play a crucial role in strengthening the cytokine storm. This means severe COVID-19 infections need to be tested for lymphocyte-to-C-reactive protein ratio, NLR and T-cell subsets [38,39]. Moreover, in COVID-19 cases platelet counts in peripheral blood were decreased significantly [40]. This agrees with the Lippi et al. study which showed a reduction of platelet count is a marker of disease conditions worsening [41].

5. SARS-CoV-2 AND CYTOKINES

CRS is a severe immune reaction caused by microbial and viral infections, including 2002 SARS, 2005 avian H5N1 influenza, and 2013 H7N9 infection [42,43,44,27]. CRS is characterized by an extreme inflammatory reaction where large numbers of cytokines are produced very rapidly. This response is an important effector in multiple organ dysfunction and acute respiratory distress syndromes [45,46,27]. In COVID-19 patients CRS is responsible for increased levels of certain chemokines and mediators, for example interleukin-6 (IL-6), tumor necrosis factor (TNF), and other pro-inflammatory cytokines which may be responsible for triggering lymphocyte deficiency [47]. In severe cases, patients who suffer from CRS are also affected by the overwhelming release of inflammatory mediators, including ILs 1β, 6, 2, 8, 4, 10, and 17, monocyte chemoattractant protein-1, induced protein 10 (IP10), IFN-γ and TNF-α [48]. In COVID-19 patients, it is unclear what triggers the production of these cytokines. Previous studies have shown macrophages, T cells, and monocytes, etc. mostly secrete cytokines including IL-6, TNF-α, and IL-10 [27,49,50], but other studies indicate that T cells are not the origin of cytokine secretion. However, T cell necrosis or apoptosis may be promoted by the cytokine storm, which would cause their reduction. Further study is required to determine if SARS-CoV-2 also triggers cytokine release in COVID-19 patients from macrophages and monocytes.

Huang et al. determined that there were significantly higher TNF-α, IL-7, IL-2, IP-10, IL-10, G-CSF, MCP-1 and MIP-1A levels in patients with COVID-19 [12]. This agrees with the result of Diao et al. [27] that showed that cytokine secretion, such as IL-6, TNF-α, and IL-10 enhanced in COVID-19 patients. The total number of CD4+ T cells, T cells, and CD8+ T cells had a negative correlation with the TNF-α, IL-10, and IL-6 levels, respectively. Diao et al. [27] suggested that the decrease in T cells in COVID-19 could involve cytokines [27]. TNF-α is classes as a pro-inflammatory cytokine, it cooperates with the TNFR1 receptor to promote T cell apoptosis and expression is elevated in aged T cells [51,52]. Studies of over 60 year old patients have shown that they have reduced numbers of T cells, which suggests that in these patients, TNF-α may be involved in T cell induction loss directly. IL-6 can contribute to host defenses when it is transiently, but promptly,

produced in answer to tissue injuries and infections; it acts by stimulation of immune reactions or acute phase responses. IL-6 dysregulation and continual synthesis can to play a significant pathological role in chronic infection and inflammation [27,53,54].

Bio et al. (2020) discovered that CD8+ and CD4+ T cells had higher PD-1 levels in the virus-infected patients, especially in the intensive care unit (ICU) patients [27]. The inhibitory cytokine IL-10 inhibits T cell proliferation and can induce T cell exhaustion. Significantly, IL-10 function inhibition has been shown to stop T cell exhaustion successfully in chronic infection animal models [55,27]. T cell exhaustion is a type of dysfunction in T cells that occurs during cancer and many chronic infections. It results in sustained inhibitory receptors expression, poor effector function, and a distinct transcriptional state when compared to memory or functional effector T cells [56,27]. Studies have shown COVID-19 patients have T cells with very high IL-10 serum levels with high TIM-3 and PD-1 levels, which are exhaustion markers, suggesting that IL-10 may be responsible mechanistically. There is also evidence that cytokines including TNF-α, IL-6, and IL-10 are involved in the reduction of T cells. Thus, for COVID-19 ICU patients, therapeutic measures are needed, and maybe new measures are needed early on to help preempt disease progression in those high-risk patients who have low T cell counts.

Using the retrospective study from Wuhan, China, of 522 COVID-19 patients and 40 healthy controls this preprint study determined that the clinical severity- and age-dependent reduction in the numbers of T cells was inversely correlated with the levels of IL-10, TNF, and IL-6 in the serum. The expression of PD-1 and TIM-3 in peripheral blood was assessed in 14 COVID-19 patients and 3 healthy controls. The CD8+ T cells from patients located in ICUs showed expression of PD1 was increased in COVID-19 patients compared with non-ICU patients and healthy controls [27]. These results suggest that as disease severity progressed, there was a related increase in inflammatory cytokine levels, which could drive T cells exhaustion and depletion [57]. Therefore, the use of relevant, potent antiviral treatments could prevent susceptible patients from getting T cell exhaustion, which could be critical to their recovery, and there is evidence that the use of Remdesivir in the US to treat a COVID-19 patient, and the use of clinical trial drugs could

have a significant potential to be used as an antiviral [27,58[59].

In 14 severe cases of COVID-19 there was serial detection of IL-1ra, IP-10, and MCP-3whihc has showed there is continuously high levels of these cytokines connected with the disease. Yang, Y et al. [60] monitored 53 clinically severe and moderate COVID-19 patients; within their study they used a multiplex screen of 48 cytokines and then correlated the results with viral loads, clinical characteristics, and lab tests. The results showed a significant increase in COVID-19 patients for 14 cytokines when compared with the healthy controls. There also was a strong association between the continuously high expression levels of three cytokines (CXCL10, IL-1 receptor antagonist and CCL7) and increased loss of lung function, increased viral load, a fatal outcome and lung injury. These results provide important insights into COVID-19 immunopathology and provide potential new avenues for therapy and prognosis for reducing fatal outcomes [60].

6. Recent COVID-19 immunotherapy

6.1 Convalescent Plasma (CP) and Intravenous Immunoglobulin (IVIg)

Infectious disease treatment and prevention may be achieved by using antibodies from naturally recovered individuals, whereas vaccine production and the immune response takes a longer time to be developed. In 2014 and 2015, the use of convalescent plasma was established and recommended for the treatment of MERS and Ebola [61,62]. The National People's Health Commission of the People's Republic of China (NHCPRC), has reported that of 157 patients with COVID-19, 91 showed significant improvements for the symptoms of coughs, fever, muscle pain, weakness and sputum, after plasma collected from rehabilitated patients was transfer to the patients during 48 h of treatment. The results also showed there was an increased lymphocyte ratio and blood oxygen saturation, and reduced virus antigen levels [61,63]. This is further supported by four critically ill COVID-19 patients that were used in case study, they received convalescent plasma and the results showed they recovered from SARS-CoV-2 , which suggest this is a promising potential therapy for severe acute COVID-19 treatment (Bin Zhang et al., 2020). After convalescent plasma treatment, and post-transfusion, there were decreased C-reactive

protein and increased number of lymphocytes when compared to the patients pre-transfusion [64]. There are two important effects of convalescent plasma that cause an improvement in patients with COVID-19, which are based on its composition; there is immunomodulatory effect that occurs due to antibodies and anti-inflammatory cytokines, and an antiviral effect that is carried out by the neutralizing antibodies (NABs) [61,65]. In COVID-19 patients, these antibodies act to help control the overactive immune system, for instance regulating the hypercoagulable state, reducing the cytokine storm, altering complement activation, and the th1/th17 ratio [61,65].

The first study on IVIG therapy in COVID-19 patients was reported by Xie et al. [66], they found that the 58 severe COVID-19 patients that had IVIG administered intravenously with an adjuvant glucocorticoid, had a reduced hospital stay length, and mechanical ventilation use when administered within 48 h of ICU admission. There was also improvement to 28-day mortality and significant clinical effectiveness [61,66].

6.2 Monoclonal Antibody

6.2.1 TNF inhibitor

Thalidomide (α-N-[phthalimido] glutarimide) is a pro-inflammatory cytokine inhibitor of IL-8 and TNF-α via NF-κB inhibition [67]. This can inhibit cell proliferation, stimulate anti- inflammation and T cells, and reduce pulmonary fibrosis and lung injury. Chen et al. [2] reported that treatment of a patient with severe COVID-19 pneumonia using thalidomide with methylprednisolone at a low-dose (glucocorticoid) 1 to 8 days after the initial treatment, improved the patient's clinical condition as they had reduced oxygen consumption, increased oxygen index, reduced lung exudation and anxiety, and relieving vomit. Days after treatment, their cytokine levels returned to the normal range, including IFN-γ, IL-10, and IL-6. Also, 5 days after treatment, there was a significant increase in their D4+T cells, B cells, T cells, CD8+T cells, NK cells, and the absolute value of lymphocytes [61,68].

6.2.2 IL-6 inhibitors

There are two FDA approved classes of IL-6 inhibitors: monoclonal antibodies against the IL-6 receptor (e.g., Tocilizumab, Sarilumab) and anti-IL-6 monoclonal antibodies (Siltuximab) [69]. Tocilizumab (Actemra®) is an IL-6 receptor antagonist approved as a treatment for elderly patients with severe active rheumatoid arthritis when used with methotrexate [70]. In COVID-19 patients there is a correlation between the severe acute pneumonia and very high levels of proinflammatory cytokines including MCP, IL-1β, TNF-α, and IL-6 caused by SARS-COV-2 [61,71,12]. It has been shown that in a male renal carcinoma patient suffering from COVID-19, two intravenous 8 mg/kg doses of Tocilizumab reduced cytokine storm and CRP [61,72]. Also, Tocilizumab treatment in severe COVID-19 patients caused a return to normal levels for clinical symptoms and findings including lung lesion CRP, number of peripheral lymphocytes and fever within a few days [61,73]. Further evidence for the effectiveness of Tocilizumab initiates from treatment of a COVID-19 positive male 60-year-old multiple myeloma patient using 8 mg/kg Tocilizumab, which decreased IL-6 levels and was highly effective in the prevention of multiple myeloma [61,23]. All these results suggest Tocilizumab is a promising, effective COVID-19 treatment which is undergoing further study. As always, there are adverse effects of treatment with Tocilizumab for COVID-19 patients, including cytopenia, acute pancreatitis, elevated ferritin and lactate dehydrogenase, hypertriglyceridemia and hypofibrinogenemia, which needs to be considered before this can be used as a widespread treatment [61,74,75].

Sarilumab (Kevzara) is a fully-human monoclonal antibody that blocks the IL-6 receptor to inhibit IL-6 signaling. To test the safety and efficacy in treatment of adult COVID-19 patients with serious complications, a phase 2/3 trial is currently being carried out [61]. There are reports of dose-dependent lab abnormalities after treatment with Tocilizumab and Sarilumab including transient and/or reversible increase in the liver enzymes, alanine and aspartate aminotransferase, and other rare occurrences of neutropenia and thrombocytopenia. There have been reports of a risk of bowel perforation and serious infections (fungal or bacterial) associated with the used of these drugs over the long-term [61].

6.2.3 IL-1 receptor antagonist

The IL-1 receptor agonist Anakinra is used to treat autoinflammatory disorders. It is a recombinant antibody that blocks that activity of both the proinflammatory cytokines IL-1β and IL-1α [76]. Anakinera has advantages over other

cytokine blockers as it has a short half-life and better safety, allowing it to be discontinued for use in critically ill patients [77]. A retrospective cohort study using intravenous Anakinera treatment in consecutive COVID-19 patients, ARDS, and hyper inflammation. The results showed high doses reduced serum C-reactive protein levels with improved respiratory function (72%), and increased survival rates (90%) compared to the standard group (56%) [61,78].

6.2.4 Complement inhibitor

Activation of complement has been suggested to cause some of the COVID-19 pathophysiology aspects of the infection, including acute kidney injury and thrombotic microangiopathy (TMA) [61]. The Diao et al. [27] study indicated in six SARS-CoV-2 patients in their renal tubules there was C5b-9 complement which could be linked to kidney complement cascade activation [27]. C5b formation inhibition by the monoclonal antibody Eculizumab prevents complement activation. This is supported by the work of Mahajan et al. [79] that showed Eculizumab was used to inhibit complement activation in a 14-year-old female to treat children-mediated AKI associated with COVID-19 infection, which lead to improved chest X-ray, clinical symptoms, and laboratory tests[61,79].

6.2.5 Anti-CD147 antibody

The humanized anti-CD147 antibody Meplazumab, has the potential to SARS-CoV infections by two mechanisms, either suppression of inflammation storm or inhibition of virus replication. Meplazumab can block virus replication and activation by acting via CD147 the spike protein receptor [80]. CD147 is also a receptor for the Cyclophilin A (CyPA) proinflammatory factor that, in response to the inflammatory stimuli, attracts and activates leukocytes to the stimulus site [81]. This means Meplazumab can inhibit CyPA interacting with CD147 to attenuate the chemotactic effect of CyPA. This is supported by the study by Bian et al. [80] that showed using Meplazumab to treat COVID-19 patients resulted in recovery of chest radiography, promotion of lymphocytopenia, increased the virological clearance rate, and decreased CRP. The short-term recovery of lymphocyte counts may be due to prevention of virus invasion which would increase lymphocytes survival, or inhibition of pulmonary organ lymphocyte accumulation and increased lymphocytes in peripheral blood [61,80].

6.3 Cytokine and Interferon Therapy

There have been many studies using type 1 interferons to try and treat COVID-19 patients as they have a broad antiviral activity. The majority of the studies showed improvement in clinical symptoms and laboratory findings [82,72]. Wang et al. [21] showed three COVID-19 patients treated with IFN-α-2b resulted in chest x-ray improvement, increased serum anti-SARS-COV-2 titration and reduced viral load [61,83]. A study in China produced the guideline that treated COVID-19 patients twice a day with vapor inhalation of 5 million unit of IFN-α combined with anti-viral drugs including Ribavirin [61] [84]. A review by Mansourabadi et al. [82] investigated 24 studies based on the efficacy of treatment of COVID-19 patients with of type 1 interferon. They found that this treatment combined with other treatments, including methylprednisolone, antiviral drugs, MSC, intravenous immunoglobulin (IVIg), and convalescent plasma (CP), improved clinical symptoms and laboratory tests. There was also improved pulmonary function, lymphocytopenia, and SARS-CoV-2 RNA to was reduced to an undetectable level [61,72,82]. There have different clinical trials registered recently to investigate treating COVID-19 patients subcutaneously with a combination of ritonavir/lopinavir with IFNβ1b and ribavirin (NCT04276688) or lopinavir/ritonavir and IFNα2b (ChiCTR2000029387) [61,85]. Treatment of the early stages of SARS-CoV-2 may be safely and easily treated with IFNβ1. Treatment of MERS-CoV and SARS-CoV with similar methods showed a mixed efficiency, but evidence from *in vitro* studies has shown that SARS-CoV-2 may be much more sensitive to treatment with IFN-I than the other coronaviruses [61,85].

6.4 JAK Signaling Inhibitors

There are several JAK signaling pathway inhibitors that are powerful anti-inflammatory agents, including Ruxolitinib, Fedratinib, and Baricitinib [61]. Inhibition of members of the numb-associated kinase (NAK) family (such as GAK and AAK1) by drugs, for example Baricitinib, *in vitro* reduce viral infection by inhibiting clathrin-mediation. There has been a lot of attention on Baricitinib as it has a high affinity for NAKs, anti- inflammatory properties, a high potential for combination therapy and an ability to ameliorate associated chronic inflammation in interferonopathies. It also has low plasma protein binding with minimal drug transporter and cytochrome P enzyme interaction. The

combination of treatment for COVID-19 patients of Baricitinib with antiviral drugs including Ritonavir or lopinavir and Ramsudavir has been suggested to reduce virus recurrence and the host inflammatory response [61,86].

Studies of the pathology and cytokine storm in COVID-19 have shown that secreted cytokines and Th17 cells are important participants. As these cell use the JAK signaling pathway for effector function and differentiation this means that Fedratinib as a JAK2 inhibitor may be beneficial for reducing COVID-19 disease mortality [61].

7. COVID 19 VACCINES STATUS AND EFFECTIVENESS

The high spread of SARS-COV-2 and its complications put scientific field in big challenge to develop treatment or protection methods for the fast transmission of this virus. As no available SARS-CoV vaccine was in the market at the start of the pandemic, this increases the obstacles required to overcome for the development of possible candidate vaccines in short time and large quantities.

Vaccine development undergoes a number of steps and phases before getting final authority approval for usage that may extend 10-15 years. It starts by tests on animal models followed by three clinical trials. Phase I applied on small number of candidates to test safety of the vaccine, Phase II where formulation and doses are determined for efficacy testing, finally Phase III as vaccine safety and efficacy tested on large population. Vaccine candidates that pass these stages successfully gets authority approval for manufactory marketing and production to be used. However, in such pandemic cases, these phases are compressed in time to meet the emergency requirement and help in controlling the spread of the virus [87].

Number of companies started their vaccine testing and get emergency authority approval for usage that have been applied in many countries. Three vaccines are authorized by US Food and drug administration up to date according to their website which are; Pfizer-BioTech, Moderna, and Janssen COVID 19 vaccines [88]. However, other countries have national approval for the usage of other vaccine candidates including Sinovac, Sputnik V, CanSinoBio, Bektop, Sinopharm and Covaxin. Each of these are different in the type of vaccine as mRNA, adenoviral vector and inactivated vaccines techniques have been used as well as their efficacy rate ranging from 95% to 50% (Nuha Alkhattabi,2021). According to the world health organization (WHO), total candidate vaccines are 287 up to date as 102 reached clinical phase and 185 still in the pre-clinical phase [89].

Number of questions remain to be answered about the effectiveness of the vaccines in the control of viral spread and the period of protection once someone have the required doses. Not much data is available from the real world to clarify these issues although up to date available data give much hope. For Pfizer-BioTech vaccine for example, in the clinical trial performed on 40,000 people it showed 95% protection from symptomatic COVID 19 however, study in Copenhagen testing the vaccine efficacy outside the clinical trial showed it was effective 64% in long term patients with 84 median age and 90% health worker that represent good news. In Israel study they found that same Pfizer vaccine provide 94% protection for people over 85 years while in UK Pfizer, and Astrazeneca both give 80% protection of hospitalization for people aged over 70 years old. Scientists now trying to understand how long immunity will last after vaccination. UK study showed that SARS-COV-2 infected people are protected for up to 7 months by natural immunity. Unpublished study in Qatar showed that natural immunity may last up to one year. However, there are concerns that immunity from vaccination would decline faster as antibodies generated in this case will not last long time and may need other vaccine boosters which are under studies [90].

8. CONCLUSION

The alteration of T-cells and cytokine levels in some severe cases of COVID-19 have been shown, but there is still speculation in the literature meaning the overall results are still inconclusive and further investigation is recommended. Moreover, the combination of anti- inflammatory therapies, involving glucocorticoids, Tocilizumab and sariluma IL-6 inhibitors, JAK inhibitors such as Baricitinib might be help in the treatment of Covid-19 patients with severe acute respiratory syndrome infection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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