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International Immunopharmacology 89 (2020) 107082

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Recent findings on the Coronavirus disease 2019 (COVID-19); immunopathogenesis and immunotherapeutics

Negin Ebrahimi[a,1], Saeed Aslani[b,1], Farhad Babaie[c,d], Maryam Hemmatzadeh[e], Ramin Hosseinzadeh[d], Zeinab Joneidi[f], Zahra Mehdizadeh Tourzani[g], Nafiseh Pakravan[h,**], Hamed Mohammadi[h,i,*]

[a] Department of International Medicine, Faculty of Medicine, Health Sciences University, Istanbul, Turkey
[b] Department of Medical Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Cellular and Molecular Research Center, Urmia University of Medical Sciences, Urmia, Iran
[d] Department of Medical Genetics and Immunology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[e] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Faculty of Nursing, Bank Meli Iran, Tehran, Iran
[g] Department of Midwifery, Alborz University of Medical Sciences, Karaj, Iran
[h] Department of Immunology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran
[i] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

ARTICLE INFO

Keywords:
Severe acute respiratory syndrome
Coronavirus-2
Coronavirus disease-2019
Immune system
Treatment
Immunotherapeutics

ABSTRACT

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) is responsible for recent ongoing public health emergency in the world. Sharing structural and behavioral similarities with its ancestors [SARS and Middle East Respiratory Syndrome (MERS)], SARS-CoV-2 has lower fatality but faster transmission. We have gone through a long path to recognize SARS and MERS, therefore our knowledge regarding SARS-CoV-2 is not raw. Various responses of the immune system account for the wide spectrum of clinical manifestations in Coronavirus disease-2019 (COVID-19). Given the innate immune response as the front line of defense, it is immediately activated after the virus entry. Consequently, adaptive immune response is activated to eradicate the virus. However, this does not occur in every case and immune response is the main culprit causing the pathological manifestations of COVID-19. Lethal forms of the disease are correlated with inefficient and/or insufficient immune responses associated with cytokine storm. Current therapeutic approach for COVID-19 is in favor of suppressing extreme inflammatory responses, while maintaining the immune system alert and responsive against the virus. This could be contributing along with administration of antiviral drugs in such patients. Furthermore, supplementation with different compounds, such as vitamin D, has been tested to modulate the immune system responses. A thorough understanding of chronological events in COVID-19 contributing to the development of a highly efficient treatment has not figured out yet. This review focuses on the virus-immune system interaction as well as currently available and potential therapeutic approaches targeting immune system in the treatment of COVID-19 patients.

1. Introduction

The 2019 outbreak of Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) causing Coronavirus disease-2019 (COVID-19) all around the globe has become a universal concern due to its rapid transmission rate and related complications, such as Acute respiratory distress syndrome (ARDS), pneumonitis, shock, respiratory failure, and death. There is a wide range for the severity of clinical manifestations from asymptomatic disease to severe respiratory failure and even death [1] (this article is a preprint and has not been certified by peer review). COVID-19 clinical signs are categorized under three types. Type I includes asymptomatic carriers with or without detectable virus. Non-severe symptomatic infection with the presence of virus is regarded as type II. Type III is represented by severe respiratory

* Corresponding author at: Department of Immunology, School of Medicine, Alborz University of Medical Sciences, Alborz, Iran.
** Corresponding author at: Department of Immunology, School of Medicine, Alborz University of Medical Sciences, Alborz, Iran.
E-mail addresses: n.pakravan@abzums.ac.ir (N. Pakravan), h.mohammadi@abzums.ac.ir (H. Mohammadi).
[1] Negin Ebrahimi and Saeed Aslani contributed equally as first authors.

https://doi.org/10.1016/j.intimp.2020.107082
Received 17 August 2020; Received in revised form 5 October 2020; Accepted 5 October 2020
Available online 10 October 2020
1567-5769/

disorder with high viral load [2] (this article is a preprint and has not been certified by peer review). The three clinical types of the disease show different behavior of the virus in terms of the host's immune system. Regardless of the disease type, immune system responds via initial innate and later adaptive responses. The resolving cases of the disease are representative of orchestrated innate and adaptive immune response. However, the damages in the non-resolving lethal cases are presumed to be due to inefficient and/or insufficient immune response. It follows to a higher viral load in the host cells and an upregulated response is the major cause of lung injury or even multiple organ failure as a result of "cytokine storm", which will be discussed further in the next sections [3–5].

COVID-19 has a typical framework of cellular profile for patients; for instance, reduced numbers of CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells are common in most of the mild and severe cases [6,7] (the article by Shi *et al.* is a preprint and has not been peer-reviewed). An increase in T helper (Th) 17 cells, neutrophil count, and neutrophil to lymphocyte ratio correlates with the severity of the disease [8].

Despite the current knowledge, there is no definitive cure for COVID-19 and many people die every day throughout the world. Having a deep comprehensive perspective of virus-immune system interaction helps us to devise effective therapeutic strategy. Accordingly, this article attempts to clarify the mechanisms of virus entry to target cells, the challenge of the immune system with the virus, and current and potential immunotherapeutic approaches in the treatment of COVID-19.

2. Risk factors associated with COVID-19 pathogenesis

According to the studies, the SARS-CoV-2 infected persons who died were mostly males, older than 70 years, diabetics, hypertensive. In addition, comorbidities, including renal diseases, heart failure, and chronic obstructive pulmonary diseases (COPD) have been reported in the infected individuals [9–11]. Patients older than 70 years, comparing to individuals with less than 50 years old, indicated a 5- to 10-fold higher risk of severe COVID-19 [12–14]. A 2-fold increase in the severe forms of disease or mortality rate have been seen in males, diabetics, hypertensive, COPD, or cases with cardiovascular diseases [12,13] (both articles are preprints and have not been peer-reviewed). High body mass index (BMI) and obesity have also been attributing to severe/lethal disease form [9]. The severity of COVID-19 was also associated with abdominal adipose tissue distribution, implying to the potential pathogenic involvement of visceral adiposity in the acute form of the disease [15]. However, evidence do not support the increased risk of severe disease or mortality due to tobacco smoking [13,16]. Interestingly, studies do not endorse the association of taking angiotensin II receptor blockers or angiotensin converting enzyme (ACE) inhibitors with COVID-19 progression [14,17].

3. Virus entry as the initial stage of the disease

The ability of an infectious agent to enter the body is a critical stage as it determines the transmission rate of the agent. Higher entering facility is associated with the higher transmission rate. The novel Coronavirus uses its envelope spike proteins to bind the human ACE2 receptor and invade the host cells, particularly in organs with high expression of ACE2, such as kidney and intestine [18]. The process of viral entry into target cells via ACE2 has been reported with varying mechanism. One study demonstrated that the viral entry is based on ACE2 shedding and involvement of Transmembrane serine protease 2 (TMPRSS2) [19] (this article is a preprint and has not been certified by peer review), while another research reported that ACE2 shedding is not a prerequisite for SARS-CoV-2 entry into the target cells [18]. Sungnak *et al.* indicated that SARS-CoV-2 entry receptor ACE2 and viral entry-associated protease TMPRSS2 are overexpressed in nasal epithelial goblet and ciliated cells, evidencing the preferential entry route by SARS-Cov-2 [20]. The receptor-binding domain (RBD) of the S protein is extremely immunogenic and antibodies binding to RBD can neutralize the virus interaction with ACE2 [21] (this article is a preprint and has not been certified by peer review). ACE2-bearing cells appear to be the most vulnerable cells against SARS-CoV-2. Alveolar epithelial type II cells constitute 83% of the lung ACE2-bearing cells. Other extrapulmonary tissues expressing ACE2 include kidneys, heart, endothelium, intestine, and also tongue [1]. The mucosa of the oral cavity is also a potential site of virus entry. Chen *et al.* reported that the spleen- and lymph nodes-associated $CD169^{+}$ macrophages of COVID-19 patients express ACE2 and SARS-CoV-2N protein and produce interleukin (IL)-6. Elevated level of IL-6 has been suggested to correlate with the disease severity [22] (this article is a preprint and has not been certified by peer review).

In a recent study based on bioinformatics methods, Li *et al.* [23] reported that human dipeptidyl peptidase 4 (DPP4 or CD26) can also play a role as a potential binding target for SARS-CoV-2 RBD. DPP4 is a serine protease that is mainly expressed in several human tissues, including lung fibroblasts, muscle, central nervous system (CNS), placenta, and immune cells like B cells, NK cells, T cells, macrophages, and dendritic cells (DCs) [24,25]. Additionally, in a mice model of ARDS (the major SARS-CoV-2 associated mortality cause), inhibition of DPP4 using sitagliptin resulted in amelioration of histological outcomes of lung injury through suppressing the inflammatory mediators tumor necrosis factor (TNF)-α, IL-1β, and IL-6 [26]. Nonetheless, experimental data revealed that SARS-CoV-2 RBD was able to bind to 293T-cells expressing human ACE2 but not to 293T-cells expressing human DPP4 [27,28]. Despite lacking of direct implications regarding the involvement of DPP4 in SARS-CoV-2 infection, data imply to the beneficial effects of DPP4 inhibitors, by modulating the inflammation and inhibiting the fibrotic function, in interrupting the progression to the hyperinflammatory condition associated with severe forms COVID-19 [29].

Major histocompatibility complex (MHC) or human leukocyte antigen (HLA) is another molecule involved in viral entry. Former studies demonstrated that there was a correlation between HLA polymorphism and susceptibility or protection against the virus [30–32]. Wang *et al.* reported that two categories of HLA alleles are associated with protectivity or susceptibility to SARS-CoV infection. To name, protective alleles include HLA-A0201, HLA-Cw1502, and HLA-DR0301, and susceptibility ones include HLA-B4601, HLA-B0703, HLA-Cw0801, and HLA-DR B11202 [32].

The third molecule involved in viral entry is CD147, which is a transmembrane glycoprotein belonging to the immunoglobulin superfamily. This molecule is also known to participate in the plasmodium invasion and tumor progression. Virus replication can partially be limited by shutting down the expression of CD147 [1].

Among the above-mentioned binding molecules, SARS-CoV-2 has the most affinity to human ACE2, making lung as the primary target tissue and the most common entry route. Sharing ACE2 as binding receptor, SARS-CoV-2 has more affinity to ACE2 than SARS-CoV. Such a high affinity accounts for rapid transmission rate of SARS-CoV-2 [33]. Overexpression of ACE2 is associated with the severity of the disease in mouse model [34]. Given the alleviating role of ACE2 in lung injury by blocking the renin-angiotensin pathway, administration of human recombinant soluble ACE2 as a competitive inhibitor and/or monoclonal antibodies against spike proteins is expected to be more beneficial instead of downregulating ACE2 [35].

To sum up, viral entry is the critical stage since the infection can be restricted at this stage with the least clinical complications. In addition, it helps us to accurately monitor and follow up the course of the disease. The impact of ACE2-virus attachment on immune response would be discussed later in this article.

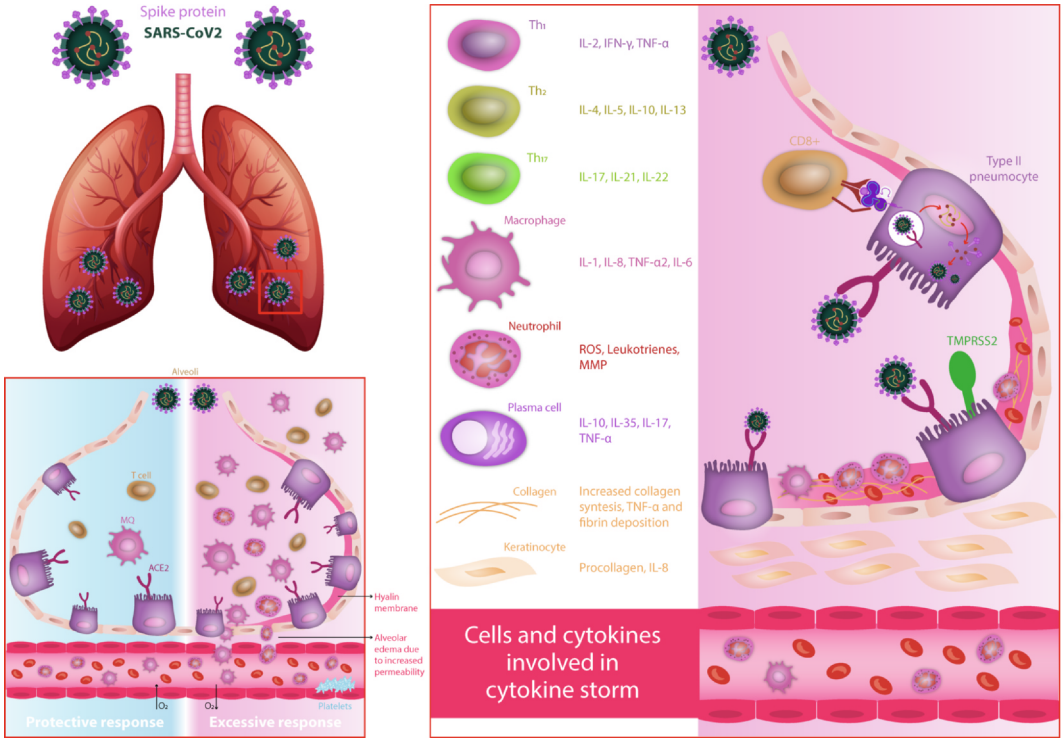

Fig. 1. Immunopathology of COVID-19. Numerous cells and molecules are involved in viral response during the infection by SARS-CoV-2. Neutrophils and macrophages are the first cellular members to start responses. Alveolar damage is caused primarily by crowded cell trafficking and hyaline membrane formation, leading to hypoxia. As the figure depicts briefly, clotting dysregulation has been detected in severe COVID-19 patients. Several mechanisms may contribute to immunothrombosis (e.g. elevated levels of pro-inflammatory cytokines). An interconnected and complex network of cells is activated during the acute phase. The most significant cytokines released by these members are illustrated. During the acute phase in alveoli, histological changes occur. Increase in the collagen synthesis and fibrin deposition is associated with hypoxic environments and makes tissues vulnerable to further injuries.

4. Innate immunity as the front line of defense against the virus

Innate immune cells along with physical barriers are early innate immune response to lung viral infections. Innate immune cells include macrophages, DCs, neutrophils, and parenchymal cells, such as fibroblasts and epithelial cells. Several receptors of innate immune cells referred to as pattern recognition receptors are responsible for detecting antigens related to the virus. Toll-like receptors (TLRs) recognizing pathogen-associated molecular patterns (PAMPs), RIG-I-Like receptors recognizing nucleic acids, C type Lectin like receptors (CLRs), and NOD-like receptors (NLRs) are pattern recognition receptors (PRRs) responsible for identifying the viral antigens [36].

A sufficiently intense innate response is required to lighten the burden of the battle for adaptive immunity. The more efficient clear up actions at the early stages of the disease, the less harmful inflammatory consequences occur. Stimulation of innate immune cells leads to secretion of inflammatory mediators, such as IL-6 and type I/III interferons (IFNs) that along with complement system play role against the viral progression in early phases [37]. However, viruses develop evasion mechanisms from the innate immunity. For example, viruses can evade the complement system wisely by removing antibody-antigen complexes from cell surfaces, decreasing Fc receptors expression, or by mimicking the complement regulatory components [38–40]. The virus-innate immune interaction crucially affects adaptive immune response against the virus and, thereby, the virus clearance and clinical outcome. Accordingly, due to complicated virus-innate immunity interactions, the immune system may sometimes delay recovery, progress the disease, or even cause death.

Upon virus entry, cytokine network is formed, among which IL-6 and IFN-I have attracted more attentions. The cytokine network is highly complicated and should be tightly regulated, and cytokine imbalance can cause severe ARDS. Inflammatory cytokines, including IL-1, IL-6, IFN-I, and TNF-α, have widely been addressed.

TNF-α and IL-1β are known as main activators of IL-6 production. IL-6 is a pleotropic cytokine that induces B cell proliferation, assists Cytotoxic T lymphocyte (CTL) activation, and involved in triggering hepatocytes to synthesize acute phase reactive proteins, such as serum amyloid A (SAA) and C reactive protein (CRP) [41]. IL-6 plays role both in pro-inflammatory and anti-inflammatory reactions. In cooperation with transforming growth factor (TGF)-β, it induces Th17 lineage and inhibits regulatory T (Treg) cell proliferation [42,43]. Having broad interactions and functions, these characteristics makes IL-6 worth focusing. Nearly all types of stromal and immune cells (B cells, T cells [44], monocytes, DCs, mast cells, fibroblasts, endothelial cells, and keratinocytes) produce IL-6 (48). Overproduction of IL-6 extends the duration of Th17 responses, leading to inhibition of immune response deviation towards Th1 response, which are required for virus clearance (described below) [45]. On this basis, IL-6 has been taken into account as a therapeutic target. Tocilizumab, an IL-6 receptor (IL-6R) antagonist (monoclonal antibody) can be used in patients with severe pneumonia and notably high levels of IL-6 [46,47]. Additionally, blocking of IL-1 and Janus kinase (JAK) appears to increase survival rate in patients with hyperinflammation during sepsis [48], also conferring the possibility of positive effects in patients with COVID-19.

IFN-I is another important cytokine in viral infections that is produced by most cells following virus entry. However, cellular sources can vary depending on the type of viral infection. Plasmacytoid and myeloid DCs are major IFN-I-producing cells [49]. IFN-I gene is activated through two main categories of detectors, including TLRs and Caspase activation and recruitment domain (CARD) proteins, including Retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) and melanoma differentiation-associated protein 5 (MDA5). TLR-3, TLR-7, TLR-8, and TLR-9 detect viral components in endosomes, while CARDs track viruses in the cytoplasm. Both types of receptors interact with PAMPs,

leading to IFN-I secretion as the initial stage of antiviral immune response [50]. Viruses are able to avoid interferon antiviral effects that in some cases make the situation more vulnerable [51]. The key role of IFN-I on the fate of infection is evidenced by a report demonstrating that IFN-I responses in the severe cases of COVID-19 patients are mainly impaired compared to the mild or moderate cases [52]. Development of evasion mechanisms by virus against IFNs response justifies the need for more specific defense mechanisms. Apart from direct antiviral activity, IFN-I also synchronizes the cellular components of innate and adaptive immunity, such as NK cells and T cell responses. The circuits among cells and cytokines become more intricate and begin deviation from normal state as more compartments of the immune system are involved.

Other cytokines and chemokine profile in COVID-19 patients have also been studied, including IL-2, IL-4, IL-8, IL-10, IL-13, IL-18, IFN-γ, TGF-β, IP-10, Monocyte chemoattractant protein-1 (MCP-1), and monokine induced by gamma interferon (MIG), which were notably elevated in acute phase of the disease, resulting in a fatal uncontrolled systemic inflammatory response (Fig. 1) [53,54]. IL-37 and IL-38 have shown immunomodulatory effects during COVID-19. IL-37 acts on mammalian target of rapamycin (mTOR), elevates Adenosine monophosphate (AMP)-activated protein kinase (AMPK), and inhibits the expression of MHC-II molecules, IL-1β, C-C motif chemokine ligand 2 (CCL2), and TNF [55]. Released by B cells, IL-38 presents similar manifestations and might be considered as a therapeutic cytokine [56].

As an arm of innate immunity, the complement system starts to act in the acute phase of the disease. Various strategies evolved in viruses to evade the complement system indicated that the complement proteins play a significant role in anti-viral defense [57]. The complement plays as a “double-edged sword” in innate immunity against pathogens. On the one hand, anaphylatoxins, such as C3a and C5a, can activate immune cells and, thereby, induce the release of various proinflammatory cytokines. Activated complement fragments, such as Membrane attack complex (MAC), C3b, and C5b induce the synthesis of arachidonic acid metabolites, including prostaglandins and leukotrienes, promoting inflammatory processes and directing the innate immunity against the virus. On the other hand, complement-mediated innate immunity activation must be fine-tuned because uncontrolled complement activation exacerbate inflammation, promotes disseminated intravascular coagulation (DIC), and finally leads to multiple organ failure and death [58,59]. A study on SARS-CoV, which can be extended and attributed to SARS-CoV-2, indicated that activation of C3, the most important and abundant protein in the complement system, deteriorates the lung dysfunction and can cause multi-organ failure [60]. In spite of having an equivalent amount of viral load, mice with C3 deficiency had fewer complications in comparison to normal mice. Gao *et al.* [61] (this article is a preprint and has not been certified by peer review) reported that lung biopsy samples from patients with highly pathogenic Coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 exhibited excessive complement activity, characterized by the enhanced C4 cleavage and complement deposition. Also, in this study elevated serum levels of C5a was observed. Blocking of C3 cleavage and its derivative products dropped the release of IL-6 from alveolar macrophages, allowing lung and affected organs to recover from the injuries. Inhibition of key components of the complement system, such as C3 and C5a, could potentially restrict the ARDS and systemic inflammation. On the other hand, complement pathway activates the coagulation pathway, resulting in thrombosis along with inflammation. In this context, cytokine storm in combination with thrombotic storm can worsen moderate cases and/or cause death in severe cases of COVID-19 [62,63].

Phagocytes (neutrophils and monocytes) and NK cells are innate immune cells. Accumulation of neutrophils producing inflammatory mediators is a threat to the host’s health [64] and higher neutrophil/lymphocyte ratio is an indicator of the severe stages of COVID-19 [65]. Additionally, NK cell frequency was reported to be significantly lower in the severe cases than that of the mild cases. Moreover, there was a functional exhaustion of NK cells as typified by upregulation of NKG2A on the NK cells [66].

5. Adaptive immunity as the final hit to clear SARS-CoV-2

The impact of innate immune system on the adaptive immune system to execute protective antiviral immunity is crucial. In some cases that the innate response may be inefficient to limit a large-scale infection, adaptive immune response is required. Recognition of viruses by innate immune cells, mainly DCs, activates adaptive immune responses. The cross-talk between innate and adaptive immune cells affects the fate of infection. Affecting the type of adaptive immune response, IL-6 and IFN-I cytokines produced by innate immune cells have also been regarded as important biomarkers in SARS-CoV, which presumably can be extended to SARS-CoV-2 [67]. The cell-mediated response performed by specific cytotoxic T lymphocytes that kill infected cells, the humoral response synthesizing antibodies by B cells, and the long-lived “memory cells” are components of the adaptive immune system fighting with the infection [68].

The initial step in the development of the adaptive immune response against viral infections is antigen presentation on the MHC II molecules to the naïve CD4+ T cells thereby differentiation to effector/helper CD4+ T cells, including Th17, Th1, or Th2 cells. Subsequently, B cells and/or CD8+ T cells are activated by helper CD4+ cell through expression of surface molecules and secretion of cytokines. Activated B cells secrete antiviral antibodies, acting against virus via several different mechanisms, including neutralization, opsonization, and activation of complement proteins. The activated CD8+ T cells termed as “CD8 + CTLs” can lyse virus-infected cells [68,69].

CD4+ T cells provide license to CD8+ T cells, contributing them to differentiate to CTLs. Additionally, they are capable of producing cytokines, including IFN-γ, TNF, and IL-2 indicating that the response during SARS-CoV infection is inclined toward Th1 profile [70,71]. The formulated vaccine against SARS-CoV tested on animal models revealed that responses pertaining to Th2 profile (such as eosinophil infiltration) are associated with a spectrum of immunopathology [72,73]. In the early stages of viral replication, IFN-γ and IL-4 downregulate the ACE2 receptor [74]. Downregulation of ACE2 naturally after virus entry or by immunomodulatory molecules affects blood pressure and fluid/electrolyte balance [75]. This finding is recommended to be taken into consideration in the projects designing vaccine for SARS-CoV-2. Furthermore, the importance of CD8+ T cells in the acute phase is irrefutable, since T cell suppression either by corticosteroid or naturally leads to T cells exhaustion, which is correlated with the deterioration of the disease. Exhaustion markers of T cells, such as Programmed cell death protein 1 (PD1) and T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), and NK cells (NKG2A) directly correlate with the levels of inflammatory cytokines and, consequently, the disease severity [76]. Exhaustion and later depletion of T and NK cells impede antiviral immunity and contribute to the infection resistance and lethal stage [77]. NKG2A, expressed on NK cells and CD8+ cells, is an inhibitory receptor and is capable of sensing MHC-I on the target cells. NKG2A blocks the cytotoxic activity of immune cells and contributes to further spreading of the viral infection [78]. NKG2A expression is amplified by IL-6 and IL-10. This heterodimeric inhibitory receptor prevents NK cells from releasing IFN-γ. On this basis, targeting this receptor by Monalizumab, a humanized IgG4, may boost the body’s anti-viral immunity [79]. Reduction in IFN-γ leads to the infiltration of neutrophils in alveoli, and the higher neutrophil/lymphocyte ratio is an indicator of the more serious stages of COVID-19 [65].

Apart from CD8+ T cells, the involvement of CD4+ T cells coincides with B cell response appearance within the first week following the onset of symptoms. The initial antibody responses are against nucleocapsid (N protein) and continue with antibody production against S proteins within 4–8 days [80]. In this context, blockade of IL-6 may

impose a defect to the humoral immunity that can be resolved by convalescent serum therapy [81]. As reported by previous studies on SARS-CoV, neutralizing antibodies for S protein are raised during the second or third week. However, in case of SARS-CoV-2, antibody response may emerge earlier. It appears that the time for neutralizing IgG to reach the peak is correlated with the severity of the disease. Based on the reports, it took about 20 days in recovered patients while it took less (about 14 days) in the expired patients [82], suggesting that the intensity of antibody response is a major drawback and cause an inefficient immunity. Comparing the mild and severe cases, it was observed that IgG and IgA levels had not significant differences, while there was a slight reduction at IgM levels in the severe cases [83]. The target of recombinant ACE2 neutralizing monoclonal antibodies is the RBD region (present in the S protein of SARS-CoV that binds to the ACE2 receptor) [84]. RBD region for SARS-CoV-2 seems to be distinct or have limited similarities to that of SARS-CoV. This finding suggests that a few monoclonal antibodies directed toward the previous subtype of Coronavirus might act against recently introduced SARS-CoV-2 [85,86]. As the virus transmits and mutates, S protein undergoes alterations which might lead to the emergence of a resistant mutant virus [87].

Polyclonal antibody therapy with the convalescent sera from recovered patients is being applied in many hospitals all around the world with promising results [88]. In utilizing antibodies as a therapeutic option, unwanted complications, such as antibody-dependent enhancement (ADE) and lung injury worsening are essential to be considered. Complications may result from imbalanced amounts of antibodies and cross-reaction. Cross-reactive antibodies may arise during previous infections reacting with another similar antigen later in another infection [89]. These antibodies following SARS-CoV-2 infection mostly target non-RBD regions of spike proteins. Results from sparse studies demonstrated that cross-reactivity was common between plasma from SARS-CoV and SARS-CoV-2, but cross-neutralization was rare [90]. Apart from neutralizing activity, antibodies interact with the innate immune system via the mechanism known as antibody-dependent cell-mediated cytotoxicity (ADCC). Binding of immune complexes to the Fc receptors of macrophages in infected regions causes further pro-inflammatory cytokine release. IL-6 and IL-1β released in this phase recruit cytotoxic T cells and neutrophils, which release leukotrienes and reactive oxygen species (ROS) that result in acute injury in the respiratory system [91]. Therefore, the major aim in designing monoclonal antibodies is suggested to be least inflammatory activity and the highest neutralizing capacity [92].

Consistent with inefficient and insufficient immune response, lymphopenia has been reported in many COVID-19 cases. This finding can be explained by the accumulation of lymphocytes in virally infected sites rather than circulating in the blood. The number of reduced cell subtypes seems to be reached in normal levels in patients recovered from the disease [93]. Although adaptive immunity is controlled precisely, management of innate immunity is difficult due to complicated interactions among innate components and infected tissues as well as its fewer specific responses. Hyperactive T cell immunity has similar consequences because of extreme innate immunity, hence immune checkpoints limit T cell responses. Immune responses against a viral infection in the lung should be developed in a way so that inhibit the infection and repair the lung tissue. In this context, regulation of anti-inflammatory mechanism, such as Treg cells and IL-10, is performed by innate and adaptive immune cells that establish immune homeostasis [94]. Efficient feedback mechanisms clear the infection as well as apoptosis immune cells that take place afterward [91]. As mentioned earlier in this paper, lymphocyte count in peripheral blood starts to restore immediately after virus clearance.

6. Histological and cellular profile in COVID-19

Severe COVID-19 is characterized by lymphocytopenia, in which levels of T cells and NK cells are below the normal range. Several hypotheses have been proposed to discuss the underlying reasons for the reduction in the total T cell population, including attraction of lymphocytes from circulating blood toward infected areas [95], direct infection of lymphocytes by the virus due to ACE2 expression [96], direct damage to secondary lymphatic organs like lymph nodes and spleen (this hypothesis requires further investigations to be approved) [22,97] (the article by Diao *et al.* is a preprint and has not been peer-reviewed), lymphocyte apoptosis due to discordant production of pro-inflammatory cytokines known as cytokine storm [98], and suppression of the lymphocyte proliferation as a result of elevated levels of acid lactic in the blood [99].

Studies reported the increase in neutrophil to lymphocyte ratio, CD4 + CCR4 + CCR6 + Th17 cells, and the higher expression of HLA-DR on the CD4+ and CD8+ T cells [100]. Chen and Qin *et al.* [93,101] reported that numbers of $CD4^+CD25^+CD127^{low}$ Treg cells and $CD45RA^+$ Treg cells were reduced in approximately all of the moderate and severe COVID-19 patients. Also flow cytometric investigation from symptomatic COVID-19 patients has shown an important infiltration of $CD14^+HLA\text{-}DR^{low}$ inflammatory monocytes and Granulocyte-macrophage colony-stimulating factor (GM-CSF)-producing cells [102] (this article is a preprint and has not been peer-reviewed). The cytotoxic granulysin and perforin proteins were also highly expressed in $CD8^+$ T cells [103]. An increase in neutrophil to lymphocyte ratio and a decrease in lymphocyte to CRP ratio are indicators of poor prognosis [104]. A bulk of studies have reported diminished frequency of NK cells in the peripheral blood of COVID-19 patients, which correlates with the disease severity [66,101,105] (the article by Song *et al.* is a preprint and has not been peer-reviewed). *Ex vivo* studies of peripheral blood NK cells from COVID-19 patients have reported diminished intracellular markers expression, including Ksp37, CD107a, granulysin, and granzyme B, proposing an impairment of cytotoxicity and production of cytokines like IFN-γ and TNF-α [66,106]. Additionally, exhaustion markers, such as Lymphocyte activating 3 (LAG3), NKG2A, and TIM3 are increased in NK cells of COVID-19 patients, suggesting that immune checkpoints on the NK cells might contribute to SARS-CoV-2 escape [66,106]. Moreover, a number of studies reported that various co-stimulatory molecules, such as CD137, Tumor necrosis factor receptor superfamily, member 4 (TNFRSF4; also known as CD134 and OX40 receptor), and exhaustion markers, such as NKG2A, Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) are upregulated on the T cells from COVID-19 patients [66,107]. Jouan *et al.* reported that numbers of invariant natural killer T (iNKT) cells and mucosal-associated invariant T (MAIT) cells were decreased in peripheral blood of patients with COVID-19 related ARDS [108] (this article is a preprint and has not been peer-reviewed). Also, this study indicated that innate T cells exhibited an altered functional profile in COVID-19 patients [108]. That notwithstanding, more studies are needed to clarify the key roles of innate T cells in COVID-19.

Atrophic and necrotic lymph nodes (secondary lymphoid tissues in general) are associated with decreased numbers of lymphocytes and notable cell degeneration are considerable in lung autopsy tissues. Immunohistochemical studies exhibited decreased levels of $CD4^+$ and $CD8^+$ T cells in spleen and lymph nodes. Damage in alveoli was correlated with the infiltrated cells mostly constituted by monocytes, macrophages, and very few $CD4^+$ lymphocytes [109]. Infiltration of the cells around blood vessels of alveoli could be resulted from endothelium damage and vasculitis [110]. The biochemical, immunological and hematological prognostic biomarkers in COVID-19 patients has shown in Table 1. Histopathology of COVID-19 could be anticipated by evaluating specific markers, including plasma D-dimer (a fibrin degradation product), ferritin, brain natriuretic peptide, creatine kinase and troponin T. Elevated levels of these markers as indicators of tissue damage are associated with poor prognosis of the disease [111]. Micro-coagulopathy and DIC are evoked by excessive cytokine response and also

Table 1
Biochemical, immunological and hematological prognostic biomarkers in COVID-19 patients.

Biomarker type	Biomarker	Result	Reference
Biochemical	LDH	Increased in severe phase	[173]*
	D-dimer	Increased risk for acute cardiac injury and DIC	[174,175]*
	NT-proBNP	Risk factor in severe phase	[176]
	CRP	The CRP levels were correlated with disease progression, and a predicted biomarker risk acute cardiac injury	[68,175]
	SAA	Increased in 80% of the patients as a diagnostic index	[69]
	Acid lactic	The suppression in lymphocyte proliferation as a result of elevated acid lactic in blood	[99]
	Troponin T	Elevated levels of troponin T as indicative of tissue damage are associated with poor prognosis of the disease	[111]
Hematological	Lymphocyte count	Severe COVID-19 is characterized by lymphocytopenia as prognostic value	[21,177]*
	NLR	Patients with NLR ≥ 3.13 were reported to be more likely to develop severe phase	[100]
	LCR	Decrease in LCR is indicator of poor prognosis	[104]
	PLR	High PLR was associated with poor prognosis	[178]
	Treg cells count	The Treg cells frequency was reduced in approximately all the moderate and severe COVID-19	[83,111]
	$CD4^+$, $CD8^+$, and NK cell counts	Levels of CD4+, CD8+, and NK cells are below the normal range and correlated with severity of COVID-19	[66,179]*
Immunological	Anti-COVID-19 antibody levels	Prolonged anti-COVID-19 IgM positivity could be used as a predictive biomarker for poor recovery. Higher anti-COVID-19 IgG levels was more found in severe phase	[93,180,181]*
	IL-6	Increased risk for respiratory failure, Correlated with severe phase of the disease and poor prognosis	[182,183]
	IL-8	Correlated with severe phase of the disease	[184]*
	IL-10	Increased in severe phase of the disease	[184]
	IP-10, MCP-3	Correlated with severe phase of the disease	[185]
	GM-CSF	The high frequency of CD14 + CD16 + GM-CSF + monocytes are found in COVID-19 patients as compared to healthy controls	[102]
	IFN-γ and IL-2	Correlated with severe phase of the disease	[186]
	IL-37 and IL-38	Immunomodulatory agents in novel corona virus infection	[55,56]
	NKG2A, CTLA-4, and TIGIT	Upregulated in T cells from COVID-19 patients	[66,107]
	CD137 and OX-40	Upregulated in T cells from COVID-19 patients	[66,107]
	PD-1, LAG3 and Tim-3	Upregulated in NK cells of COVID-19 patients	[106]

LDH; lactate dehydrogenase, ***NT-proBNP;*** N-terminal-pro brain natriuretic peptide, ***CRP;*** C-reactive protein, ***SAA;*** Serum amyloid A, ***NLR;*** Neutrophil to Lymphocyte Ratio, ***LCR;*** Lymphocyte to C-reactive protein Ratio, ***PLR;*** Platelet to Lymphocyte Ratio, ***Treg;*** T Regulatory, ***NK;*** Natural killer, ***IL;*** Interleukin, ***MCP-3;*** Monocyte chemotactic protein-3, ***GM-CSF;*** Granulocyte-macrophage colony-stimulating factor, ***INF;*** Interferon, ***CTLA-4;*** cytotoxic T-lymphocyte-associated protein 4, ***TIGIT;*** T cell Immunoreceptor with Ig and ITIM Domains, ***PD1;*** Programmed cell death protein 1, ***LAG-3;*** Lymphocyte-activation gene 3, ***TIM-3;*** T-cell immunoglobulin mucin-3.

* Articles are preprints and have not been peer-reviewed.

hypoxemia [112]. Despite marked elevation of D-dimer levels in severe cases, DIC contributes to late stages in rare cases of COVID-19. Anticoagulant treatment appears to be associated with the ameliorating course of the disease in these cases [113]. Recently, several studies represented that COVID-19 could result in autoinflammatory and autoimmune disorders, such as pediatric inflammatory multisystemic syndrome like Kawasaki disease, Kawasaki-like disease, shock syndrome, toxic shock syndrome, macrophage activation syndrome, and myocarditis in children [114–117] (the article by Toubiana *et al.* is a preprint and has not been peer-reviewed). Future studies should aim to disclose the fundamental molecular mechanisms that result in the mentioned disorders following COVID-19.

7. Gut microbiota and COVID-19

Even though alveolar epithelial cells have been known to be the major target for SARS-Cov-2, studies revealed the presence of SARS-CoV-2 RNA in the stool samples of COVID-19 patients [118,119]. The intestinal epithelial cells have also been indicated to express ACE2 receptors [120], implying to the possible implication of gut microbiota in the lung-gut axis during the pathogenesis of COVID-19. Gut microbiota has been shown to be impaired during respiratory viral infections [121]. Moreover, aging has been associated with diminished diversity in the gut microbiome [122], and since higher mortality rate has been reported in old age patients with COVID-19 [123], there might be a connection between SARS-CoV-2 related mortality and gut microbiota.

Commensal microorganisms in the gut play an essential role in balancing the pro-inflammatory responses (like those by Th17 cells) versus anti-inflammatory responses (such as Treg cells) [124]. A healthy gut microbiome in patients with SARS-CoV-2 infection might modulate the immune responses toward a protective state and avoid adverse reactions against lung tissue. Dietary composition is involved in determining the gut microbiota profile and hence impresses the health status. In addition, probiotics have been associated with beneficial effects in modulating inflammatory settings and controlling the innate immune responses through TLRs signaling pathways [125]. Moreover, administration of probiotic bacteria, such as *Bifidobacterium lactis*, *Lactobacillus rhamnosus*, and *Bifidobacterium* breve in mice resulted in development of Treg cells [126].

Therefore, providing probiotics by diet might be beneficial in establishing a proper state of gut microbiota profile and probably lung microbiota, leading to orchestrating immunity. Improving gut microbiome composition through personalized nutrition and supplementation might provide prophylactic approach to reduce the detrimental manifestations of the COVID-19.

8. Current immunotherapeutic prospective for COVID-19

Devise of therapeutic approaches requires a comprehensive perception of the pathological mechanism and chronological stages of the disease. In addition, determining the stage of the disease is necessary prior to applying a treatment. Administration of a medication early in the symptom onset might not be beneficial and even could be deleterious later in the acute phase. The immunotherapeutic approaches can hinder virus entry, replication, and/or the immune system behavior.

Chloroquine (CQ) and hydroxychloroquine (HCQ) are medications used as prophylaxis and also treatment objectives in patients with malaria, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). CQ and HCQ possess antiviral activity on a wide spectrum of viruses, importantly on SARS-CoV-1, which share common features

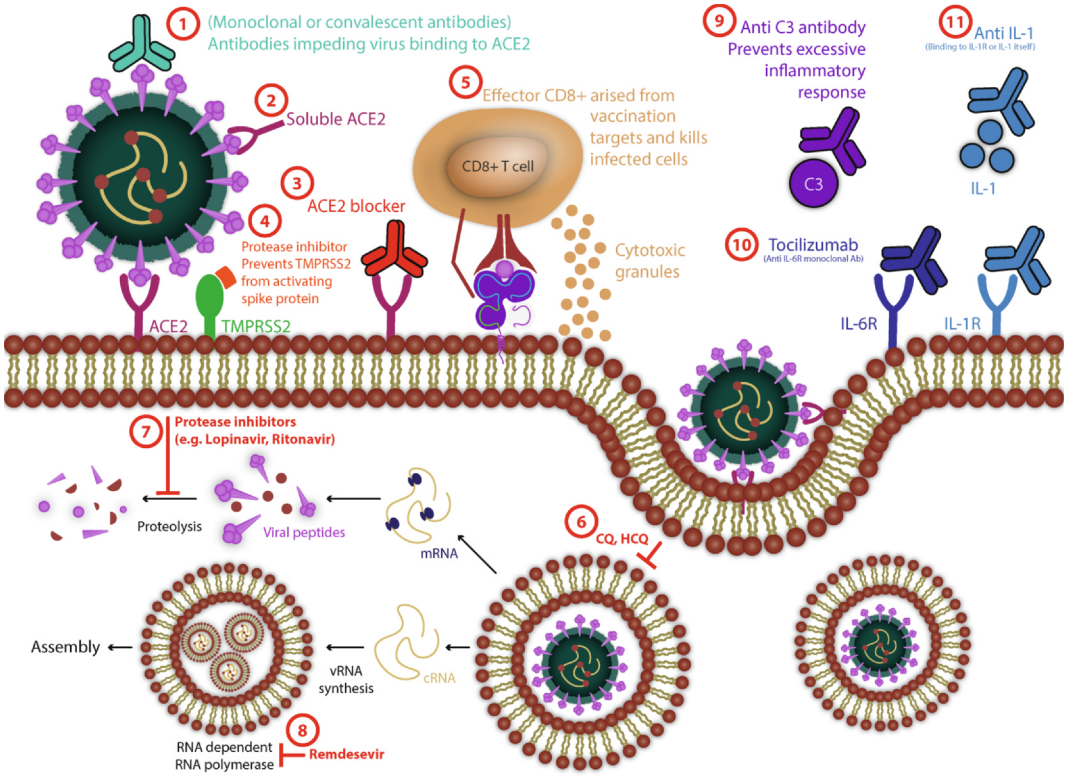

Fig. 2. Currently proposed methods to prevent or cure COVID-19. The first stage of a viral infection is the entry phase. SARS-CoV-2 infects the ACE2 and TMPRSS2 expressing cells. ACE2 and TMPRSS2 have been demonstrated to play a major role in opening the gates for this virus. The figure illustrates the proposed strategies in restricting virus entry. Blocking spike proteins by the means of monoclonal antibodies, employing soluble ACE2 as a competitive agent for normally expressed ACE2 on cells, hindering ACE2 itself or suppressing the TMPRSS2 from activating the spike protein are theoretically efficient strategies. Promoting immune response in the protective phase and downregulating it in the acute phase are established as the most effective approaches to minimize the complications caused by divergent immune responses. In addition, vaccination can boost the cytotoxic activity exerted by CD8+ T cells, which in turn prevents the body from manifesting advanced symptoms. Occluding the viral replication cycle in several phases is the basis for developing many anti-viral drugs. The normal process of vesicle formation, RNA polymerization, proteolysis, and assembly of viral compartments are crucial stages that have been targeted by anti-viral drugs.

with SARS-CoV-2. QC and HCQ interfere with viruses in the stages of entry, viral replication cycle, and post-translational modification of viral proteins [127,128]. These two medicines can also affect cell signaling and the production of pro-inflammatory cytokines [110]. However, clinical trials have yielded no beneficial effects of HCQ in the treatment of COVID-19.

In the single arm protocol from early March to March 16th trial by Gautret *et al.*, 20 French COVID-19 patients received 600 mg of HCQ daily and their viral load in nasopharyngeal swabs was tested each day. This trial revealed that there was a significant reduction of the viral carriage at day 6 compared to controls. Additionally, a treatment regimen of HCQ and azithromycin was observed to be more efficient for virus elimination [129]. Nonetheless, this trial suffered from a number of limitations, including small sample size, dropout of six patients from the study, non-randomized and open-label design, and follow-up of small number of outcomes in a long-term period. Molina *et al.* replicated the trial in 11 French COVID-19 patients in another hospital, and the patients received 600 mg/day HCQ for 10 days along with 500 mg day 1 and 250 mg days 2 to 5 of azithromycin. Quite conversely compared to the trial by Gautret *et al.*, Molina *et al.* observed that combination of HCQ and azithromycin did not have strong antiviral activity or clinical benefits in severe COVID-19 patients [130]. Furthermore, the trial of 30 treatment-naïve patients with COVID-19 at Shanghai Public Health Clinical Center also was not able to report beneficial effects of HCQ. The viral clearance and clinical outcomes, including temperature normalization, duration of hospitalization, and radiological progression had no difference on day 7 in patients after receiving 400 mg/day HCQ for 5 days plus conventional treatments compared to the control group receiving only the conventional treatments [131]. In another trial in China, 75 COVID-19 patients received a loading dose of 1200 mg/day HCQ for three days followed by a maintenance dose of 800 mg/day HCQ for two weeks in patients with mild to moderate disease and three weeks in patients with severe disease. The trial reveled that HCQ not only was inefficient, but also was associate with higher rate of adverse events [132]. A randomized, double-blind, placebo-controlled trial across the United States and Canada evaluated the efficacy of HCQ as prophylaxis after exposure to SARS-CoV-2. The subjects were those that had exposure to someone with confirmed COVID-19 at a distance of less than 6 ft for more than 10 min. The results revealed HCQ was not able to prevent COVID-19 development in the viral-exposed individuals [133]. The post-exposure prophylactic effect of HCQ is also under consideration in COVID-19 patients from Sri Lanka [134]. Overall, other than one study in French with small sample size, resting trials do not support the therapeutic effect of HCQ in the COVID-19 patients or prophylactic effects in the post-exposure individuals. However, a number of trials are currently under implementation to disclose the bona fide effect of HCQ in the COVID-19 patients and we need to wait for the results to come up with a valid conclusion on the efficacy of HCQ.

Pfaender *et al.* reported that Lymphocyte antigen 6 complex locus E (LY6E) interfere with COVID-19 spike protein-mediated membrane fusion [135]. Soluble ACE2 has also been suggested as a neutralizing agent to interrupt virus entry [136]. Apart from targeting virus by plasma therapy and inhibitors of the virus replication (such as remdesivir that inhibits viral RNA synthesis, and the trials reported that it might be efficient [137] and inefficient [138] in treating COVID-19 patients), most of the treatments are based on alleviating symptoms of the cytokine release that continues with multiple organ failure in severe

case. As we mentioned earlier, cytokine storm is caused by excessive release of inflammatory cytokines like IL-6. Patients with severe manifestations exhibit higher levels of IL-2, IL-7, IL-10, Granulocyte colony-stimulating factor (G-CSF), IP-10, MCP-1, Macrophage inflammatory protein-1α (MIP-1α), and TNF [101]. Damages caused by inflammatory responses could be attenuated by inhibitors of proinflammatory cytokines, related receptors, and the complement system. These approaches appear to be beneficial as shown in numerous clinical trials [56,71,139]. While administering anti-inflammatory agents, the balance between pros and cons should be taken into consideration.

One of the important questions that should be addressed is that whether anti-inflammatory regimen can potentially reduce the capacity of the immune system to fight with the virus, whose answer is not definite. The issue can be explained by an example; JAK inhibitors are a group of anti-inflammatory agents that inhibit the production of IFN-α, which is an important factor in combating the virus, while other modulatory agents such as anakinra (IL-1 receptor antagonist), tocilizumab (IL-6 inhibitor) and intravenous immunoglobulin seems to be less deviated from their main function (Fig. 2) [140,141]. Additionally, a meta-analysis of trials revealed that there was a significant difference in mortality rate between COVID-19 patients receiving tocilizumab (132/675, 19.5%) and the control group (283/1000, 28.3%) [142], implying to the positive effects of tocilizumab over its adverse side effects regarding suppressing the immune system in the receiving COVID-19 patients.

Glucocorticoids can also alleviate fever and pneumonia, however by affecting the lymphocyte population. They exhibit some adverse effects and delay the recovery process during SARS [143–145]. If glucocorticoid should be used in infectious conditions like sepsis, it is suggested to be in low dosage and short term [146]. Given the interconnection between inflammation and coagulation, to resolve the thrombotic storm as mentioned before, anticoagulant therapy, which also have anti-inflammatory effects, can be performed in COVID-19 patients [147].

As mentioned before, production of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1α, G-CSF, and GM-CSF has been considered as a major mechanism involved in severe cases of COVID-19 [5,148]. On this basis, induction of trained immunity as prophylactic strategy has also been proposed. A prominent approach of such strategy could be achieved by Bacillus Calmette–Guérin (BCG) vaccine that develops a non-specified partial immunity against SARS-CoV-2 [149]. Trained immunity is associated with metabolic and epigenetic changes that promote innate response. This was based on initial observation indicating that BCG has shown some protection against experimental viral infection [150]. Moreover, epidemiological investigations have suggested that countries and regions with mandatory BCG vaccination for the population have lower cases of infections and mortality rate due to COVID-19, presumably based on trained innate immunity [151–153]. This view has not been restricted to BCG and the issue regarding oral polio vaccine has also been proposed [150].

In patients with impairment in the epithelium of the respiratory system, mesenchymal stem cell (MSC) therapy has been tested that exhibited promising results [154]. MSCs need to be activated by interferon (IFN)-γ to exhibit their anti-inflammatory properties [155].

Administration of hyaluronidase-2 has also been considered in order to clear the lungs from the thick jelly layer and alleviate the respiratory symptoms [156]. IL-1 and TNF-α are important inflammatory cytokines that induce hyaluronan synthase-2 (HAS2) in fibroblasts, CD31 expressing endothelium, and Epithelial cell adhesion molecule (EpCAM)-expressing alveolar cells [156]. Hyaluronan absorbs water in the alveolar epithelium and exacerbates the lung damage, and reduces the functional capacity of the respiratory system [5].

To sum up, cells and other compartments taking part in virus clearance must be kept intact or boosted on its best condition. On this basis, the cells and molecules involved in the acute inflammatory phase should be put under control to the levels so that they can continue their antiviral activity and act against other opportunistic infections. Targeting IL-17A, for instance, facilitates the infection by candida species. Furthermore, bacterial infections are more probable in patients treated with IL-6 and TNF inhibitors. JAK1 and JAK3 inhibitors reduce the potency to combat against viral infections due to interference with type I IFNs, IL-2, IL-15, IL-21, and IFN-γ. Roschewski *et al.* reported that targeting extreme host inflammation with a Bruton tyrosine kinase (BTK) inhibitor is a treatment strategy in severe COVID-19 patients [157]. The IL-15 immunotherapy may be a potential strategy for COVID-19 via upregulating of innate immune responses, such as the activation and induction of CD8+ T cells, NK cells and Treg cells to neutralize Th2 cytokine storms [158].

9. Vitamins modulating immune system during COVID-19

The activity of the immune system is affected by the elements present in the microenvironment, among which nutrient and more specifically vitamins play outstanding roles. Vitamin A and D influence the immune system directly [159].

Vitamin D (1,25(OH)2VD3) exerts its immunomodulatory effects by inhibiting T cell proliferation [160], expression of IL-2 [161], and IFN-γ [161]. 1,25(OH)2VD3 directs differentiation of Th cells toward the Th2 responses by inducing of IL-4 production [162] and blocking differentiation to Th1 responses by suppressing the IL-12 production [163]. Given the downregulatory effects on IL-6 and IL-23, 1,25(OH)2VD3 inhibits the differentiation of naïve T cells to Th17 cells. Vitamin D also raises the production of IL-10 along with downregulation of IL-12 synthesis, leading to deviation of Th1 response to IL-10-producing Treg cells [162]. In addition to its modulatory effects on T cells, 1,25(OH)2VD3 also downregulates B cell proliferation and consequently IgG production by indirect affecting on the immunologic synapse in the antigen presenting cells (APCs)-Th cells interface [160]. Although vitamin D exhibits inhibitory function on adaptive immunity, it has stimulatory effects on the innate immune responses [164].

In contrast to vitamin D, vitamin A (Retinoic acid) promotes cytotoxic capability of the immune system and also T cells expansion that may be beneficial responses in case of COVID-19. It assists signal transduction in T cells and enhances the secretions of IL-2. The definite effect of retinoic acid on B cells is not clear, however, it presumably inhibits B cells apoptosis [165]. Similar to vitamin D, retinoic acid also aids differentiation of T cells towards Th2 response. In addition, vitamin A stimulates the production of type I interferon, thereby, exerting antiviral activities [166]. In addition, vitamin A confers a therapeutic potential in autoimmunity by modulating the Th17/Treg balance [167,168]. Taking together, vitamin A might be beneficial in COVID-19 patients by modulating immune system toward an anti-inflammatory setting during remission phase of the disease and by stimulation of antiviral state.

Other vitamins including C, E, and B complex have also been reported to be involved in some nonspecific reactions. For instance, vitamin C exhibits antioxidant activity and vitamin E acts as a scavenger or key cellular regulator. There are scattered studies reporting that vitamin C and E perform anti-inflammatory activities. Furthermore, vitamin E has been reported to stimulate the production of type I IFN in the cells [169,170].

Briefly, vitamins are necessary for the normal function of immune system. Vitamin deficiency in patients with chronic infections, such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human immunodeficiency viruses (HIV) have reported to be associated with a higher viral replication rate and dysregulated cytokine response. Additionally, insufficient levels of serum 25(OH)D has been associated with respiratory disorders and promoted proneness to acute respiratory infections [171], which have been attributed to main death cause in COVID-19 patients. Therefore, vitamins, particularly vitamin D supplementation may potentially have beneficial effects in soothing the manifestations of respiratory syndrome in COVID-19 patients [172]. However, no direct evidence is currently available on the efficacy of

vitamins in COVID-19 patients and anti-viral effects of vitamins on SARS-CoV-2 infection require further investigations.

10. Conclusion

This review briefly presented the interaction among SARS-CoV-2 and various compartments of the immune system. We discussed the mechanism of infection in different stages of the disease and proposed the most applicable and favorable strategies in order to restrict the virus and its following complications. Primarily prophylactic strategies and further regulating host immune response, monitoring the function of several organs (for instance lungs, kidneys, and heart) and systems (for instance coagulation system) may be as important as targeting the virus itself. Ongoing studies regarding treatment procedures have some contradictory result; we considered the findings that there were most consensuses on. However, it should be noted that a number of studies referenced in this review article are currently in the pre-print step and not completely peer-reviewed, subjecting some considerations before reaching the final point. The most devastating response to viral infection was mentioned to be excessive inflammation and cytokine release syndrome. The framework to control these immoderate reactions seems to be constant, however, capable of being progressed. In scheming treatment protocols, several factors regarding virus (mutations, viral load, viral titer, and evading mechanisms) and host (age, gender, nutrition, HLA genes, the efficiency of the immune response) are suggested to be considered. In designing a proper vaccine, researchers are being contributed by previous studies on SARS and MERS and take advantage of studying evolved and properly transformed immune cells and their related responses, such as B cells and their related neutralizing antibodies. Further investigations are required in order to reach precise and the most efficient ways to combat this global health issue.

Author contributions

Negin Ebrahimi; Performed literature search, prepared the draft of the paper, and read the manuscript critically.

Saeed Aslani; Performed literature search, prepared the draft of the paper, and read the manuscript critically.

Farhad Babaie; Participated in manuscript drafting and read the manuscript critically.

Maryam Hemmatzadeh; Participated in manuscript drafting and read the manuscript critically.

Ramin Hosseinzadeh; Draw the figures and read the manuscript critically.

Zeinab Joneidi; Participated in manuscript drafting and read the manuscript critically.

Zahra Mehdizadeh Tourzani; Participated in manuscript drafting and read the manuscript critically.

Nafiseh Pakravan; Developed the main idea, designed the work, and read the manuscript critically.

Hamed Mohammadi; Developed the main idea, designed the work, and read the manuscript critically.

Funding

This study was financially supported by a grant from the Alborz University of Medical Sciences, Karaj, Iran (Grant No. 1398-1-2-3721).

Declaration of Competing Interest

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.

Acknowledgements

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.107082.

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