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Immunotherapeutic approaches to curtail COVID-19

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ABSTRACT

COVID-19, the disease induced by the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has imposed an unpredictable burden on the world. Drug repurposing has been employed to rapidly find a cure; but despite great efforts, no drug or vaccine is presently available for treating or prevention of COVID-19. Apart from antivirals, immunotherapeutic strategies are suggested considering the role of the immune response as the host defense against the virus, and the fact that SARS-CoV-2 suppresses interferon induction as an immune evasion strategy. Active immunization through vaccines, interferon administration, passive immunotherapy by convalescent plasma or synthesized monoclonal and polyclonal antibodies, as well as immunomodulatory drugs, are different immunotherapeutic approaches that will be mentioned in this review. The focus would be on passive immunotherapeutic interventions.

Interferons might be helpful in some stages. Vaccine development has been followed with unprecedented speed. Some of these vaccines have been advanced to human clinical trials. Convalescent plasma therapy is already practiced in many countries to help save the lives of severely ill patients. Different antibodies that target various steps of SARS-CoV-2 pathogenesis or the associated immune responses are also proposed.

For treating the cytokine storm induced at a late stage of the disease in some patients, immune modulation through JAK inhibitors, corticosteroids, and some other cognate classes are evaluated.

Given the changing pattern of cytokine induction and immune responses throughout the COVID-19 disease course, different adapted approaches are needed to help patients. Gaining more knowledge about the detailed pathogenesis of SARS-CoV-2, its interplay with the immune system, and viral-mediated responses are crucial to identify efficient preventive and therapeutic approaches. A systemic approach seems essential in this regard.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emerged betacoronavirus, is responsible for coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China in December 2019. SARS-CoV-2, the third fatal virus of its group, is an enveloped positive-sense, single-stranded RNA virus [1]. While the other viruses of this family induce only mild cold symptoms, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the two other virulent betacoronaviruses, have been presented with higher fatality rates than SARS-CoV-2. On the other hand, SARS-CoV-2 has shown a higher transmission rate and therefore a wider spread around the globe [2].

The burden of coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been very huge on health, economy, and many other aspects of life. It has already claimed more than 750,000 lives (as of 15 August 2020 according to WHO COVID-19 dashboard at https://covid19.who.int/). The urgency of this threat has prompted scientists in many countries to seek solutions through drug repurposing and repositioning of the previously approved drugs, while the fast-tracking of vaccine and drug development are seriously followed. However, some of the repurposed candidate drugs have already failed in some clinical trials [3].

Some antiviral drugs, developed for other similar viruses, are suggested, which may inhibit the cell entry or replication of the virus [2]. On the other hand, supporting the immune system's potential to function properly and fight with the virus is another viable strategy. Normalization of the dysregulated immune responses or even their suppression at the final stages of the disease may also be required [4].

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Although the role of the immune system in overcoming COVID-19 is indisputable, and many therapeutic and preventive approaches implicate modulation of the immune system activity, there are still many questions to be answered in this regard. For instance, the pattern of cytokine secretion during the disease course has been the subject of vast investigations. In this review, the pathogenesis of SARS-CoV-2 and its interplay with the immune system are briefly stated. A classification of possible immune-based approaches to combat COVID-19 is presented with a focus on convalescent plasma therapy, antibodies, and immunomodulators.

2. Pathogenesis of SARS-CoV-2 in brief

SARS-CoV-2 enters the lungs through the nasopharyngeal mucosal membrane and infect alveolar macrophages and type I and II epithelial cells in the lungs [5]. The most prominent way of viral entry was shown to be through the attachment of S protein and angiotensin-converting enzyme 2 (ACE2) receptors, which may be enhanced through some proteases such as a serine protease called TMPRSS2 (transmembrane protease, serine 2) or Cathepsin L/B (CTSL/B) [6]. Another serine exopeptidase receptor, called dipeptidyl peptidase 4 (DPP4) or cluster of differentiation 26 (CD26), was also shown to provide additional interactions with SARS-CoV-2 spike beside the ACE2 receptor [7]. It was revealed that the virus can also enter the cell through clathrin-dependent and -independent endocytosis pathways. For instance, SARS-CoV-2 may attack lymphocytes through the JAK-STAT pathway [8].

COVID-19 patients manifest mild to severe symptoms, including fever, non-productive cough, dyspnea, malaise, fatigue, lymphopenia, and pneumonia 2–14 days after the viral attack. Moreover, laboratory results including leucopenia, elevated C-reactive protein (CRP), and higher erythrocyte sedimentation rate (ESR) are detected. A wide range of other clinical manifestations has been observed in COVID-19 involving different organs, namely heart, eyes, nose, brain, pancreas, kidney, and bladder. As reported, 7–14 days upon the manifestation of the initial symptoms of the disease, the virus may cause a second attack and an aggravation of the disease symptoms in which severe pneumonia, ground-glass opacity, acute cardiac injury, and RNAaemia are observed [9]. Moreover, patients who succumbed to COVID-19 represented a higher level of neutrophils, D-dimer, blood urea nitrogen (BUN), and creatinine than the survivors [10,11].

3. Immunotherapeutic approaches against SARS-CoV-2 based on its immunopathology

Viral antigens are presented to T cells and B cells via major histocompatibility complex (MHC) on antigen-presenting cells (APCs), thus innate and adaptive immunities are activated. Innate immunity response is initiated by interferon secretion from the infected cells in viral infections for signaling to other cells and making them ready for the battle [4]. SARS-CoV-2 is found to antagonize the induction of type I interferons (interferon-alpha and -beta) [12,13] thereby evading the innate immune system defense [14]. Moreover, it was shown that the immune system decision between Th1 response (cellular response) or Th2 response (humoral response), which is affected by the cytokine pattern, determines the viral infection control. In fact, it was reported that some infections were well controlled by a Th1 response, and this response was observed in 20 recovered COVID-19 patients [15]. SARS-CoV-2 was found to suppress antigen presentation through the down-regulation of MHC class I and II molecules, which may lead to the impediment of T cell-mediated immune defense [16].

In the second attack phase of the disease (usually one or two weeks after the presentation of the first symptoms), the level of lymphocytes drops dramatically, and the cytokine storm occurs. Cytokine storm is an uncontrolled release of inflammatory cytokines, including IFN-α, IFN-γ, GM-CSF, G-CSF, IL-1ß, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-ß, and chemokines, particularly CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10. The cytokine level reduces as the patient recovers. Cytokine storm has been recognized as the main cause of acute respiratory distress syndrome (ARDS), which causes lung injury and multiple organ failure. Taken together, the immune system is highly impaired in critically ill COVID-19 patients.

Given the role of the immune system in host defense, immunomodulation could be regarded as an important strategy to curtail COVID-19 considering the patient's immune system condition at various phases of the disease. Such immunomodulatory interventions can be achieved using vaccines, interferons, convalescent plasma, anti-inflammatory agents, antibodies, and other classes of immunomodulators, which are described in the following.

4. Interferons

The suppression of interferon I-mediated immune responses by SARS-CoV-2 is already confirmed [12,13]. Although interferon was shown to fight against the virus and is suggested to treat the disease [17], some contradictory data demonstrated that interferon may enhance ACE2 expression and thus viral entry [18]. On the other hand, positive results were found by using interferons type I, including interferon-beta-1a in several clinical trials [19]. The difference in the route of administration, either subcutaneous (s.c.) and intravenous (i.v.), was proposed as a reason for the diverse effects reported about interferon beta-1a in some studies [20]. The outcomes of the investigations on interferon therapy in COVID-19 were presented in some other publications [17,19,20] and as a systematic review [21]. Interferon-beta is already being examined in a combination protocol in the international clinical trial launched by WHO, called the "Solidarity" trial, in the partner countries [3].

5. Active immunization using vaccines

Vaccines are believed as the ultimate protection for saving the public from the novel virus. The lack of previous exposure of the human immune system to SARS-CoV-2 [22] is regarded as the major contributor to its high risk. Hence, active immunization through vaccines could prepare the body to resist against this infection. Very soon after finding the virus genetic sequence, vaccine development was started and followed with unprecedented speed by several research groups and pharmaceutical companies. Huge investments are dedicated by several public and private bodies to advance this project [2].

As of 13 August, 29 candidate vaccines have entered the clinical phase, eight of which are already in phase 2 or 3. In addition, 138 candidate vaccines are in preclinical development. The six pioneer vaccines have already entered in clinical trial phase 3, including ChAdOx1-S, developed by the University of Oxford in collaboration with AstraZeneca Pharmaceutical Company, an inactivated vaccine from Sinovac, two RNA-based vaccines, one by Moderna and the other through a collaboration of BioNTech, Fosun Pharma, and Pfizer; two other inactivated vaccines and one with an adenovirus vector are also under clinical trial in China (accessed on https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines).

Various platforms are employed in these investigational vaccines, including inactivated, killed or weakened pathogen, non-replicating viral vector, RNA, DNA, VLP (virus-like particle), and protein subunit structures. There also some replicating viral vector-based vaccines under development. Each of these platforms has its own advantage and limitations. For instance, while DNA and RNA vaccines are intensively studied mainly because of their rapid development, easy production, and safety, their large-scale production might need more time to set up, due to novelty and lack of previous experience in their commercial production. Additionally, more than one dose of these vaccine types is required for the immunization because of their short half-life [23]. This topic is reviewed in details elsewhere [23–25].

All in all, vaccine development is a time-consuming process.

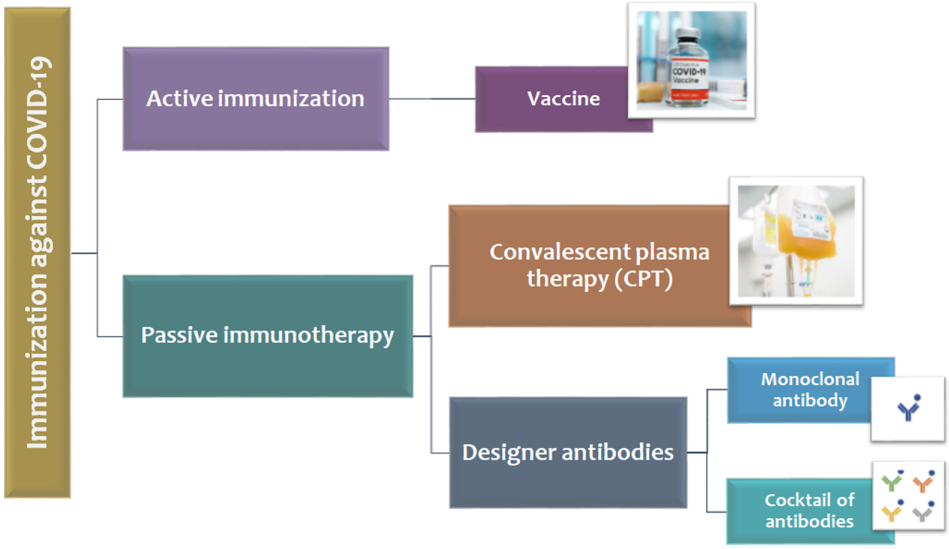

Fig. 1. Immunization approaches against COVID-19. Active immunization is provided through vaccines, which are still under development for COVID-19. Passive immunization can be performed via natural antibodies using convalescent plasma therapy (CPT) or antibodies that are manufactured. In CPT, neutralizing antibodies derived from a hyperimmune patient would be administered to a COVID-19 patient through plasma transfusion. This approach is already being used and investigated in many countries with acceptable levels of success. On the other hands, different polyclonal or monoclonal antibodies could be produced via using hybridoma cell-lines, animals, or cell-free protein synthesis, which may be administered in patients as a monoclonal antibody or a cocktail of antibodies.

Moreover, the induction of memory in the immune system is still under question. Therefore, despite preliminary promising results, the efficiency of the investigational vaccines should be confirmed in large clinical trials.

6. Passive immunotherapy

Considering the lack of an approved drug or vaccine against SARS-CoV-2, taking advantage of a helpful alternative intervention is an urgent need [26–28]. Passive immunotherapy via neutralizing antibodies has been considered as a possible strategy for defeating COVID-19 apart from anti-viral therapeutics and vaccines (Fig. 1). Antibodies can be either isolated from a convalescent patient or produced in a lab [29]. These two approaches would be discussed in more detail in the following.

6.1. Convalescent plasma therapy (CPT)

Neutralizing antibodies derived from a hyperimmune patient through plasma transfusion is the most prevalent and accessible empirical approach used to treat several viral infections previously. This method, so-called convalescent plasma therapy (CPT), is also considered as a viable therapy for COVID-19 [30–32].

It has been used to reduce the hospital stay and the mortality rate of critically ill patients with severe acute respiratory syndromes [32,33] and was found beneficial in some previous epidemics of infectious diseases [34]. The use of this approach was suggested for the first time during the outbreak of Spanish influenza (pandemic of 1918–1920) [33]. Subsequently, plasma transfusion was recommended as a safe and effective way for the prevention or treatment of the Ebola virus in 2014 and also several other severe viral infections, including MERS, SARS-CoV, and avian influenza A [35,36]. In fact, neutralizing antibodies in the convalescent plasma (CP) could suppress the viremia through binding to the external antigens of the viruses and blocking their entry into the host cells [34,37]. The effectiveness of CPT could vary according to the type of microorganism, it's pathogenesis, and treatment protocols, such as timing, dosing, and volume of administration [33].

According to the previous evidence for plasma therapy of other coronaviruses, such as SARS-CoV and MERS, the early transfusion of CP can probably be more effective and improves the survival rate of critical COVD-19 patients at the early disease stage. It could be explained by the fact that in most viral infections, viremia rises in the first week of the disease [37,38]. It should be noted that CPT may not be useful for mild or end-stage patients. Indeed, CPT is not able to significantly reduce the mortality rate among end-stage patients because of their disease severity. On the other hand, mild patients can be self-recovered, and CPT would not be required [39].

The titer of SARS-CoV-2 neutralizing antibodies in the CP could be another important factor to increase the treatment efficacy. Although, the antibodies level in the donor plasma before transfusion is not determined, some studies indicated that the specific IgG increases about three weeks after symptom onset and peaks at week 12. Therefore, the CP from donors who are at week 12 after the initiation of the symptoms is predicted to be more efficient [27,40].

Generally, patients with primary and secondary antibody deficiencies, need intravenous immunoglobulin (IVIG) treatment as the standard replacement therapy [41]; and historically, administration of IVIG has been one of the important treatments in immunodeficient patients [42]. These patients are considered as a high-risk group, which can encounter several severe complications if infected with SARS-CoV-2 virus [43]. Therefore, an effective treatment is required to help such patients survive. CP extracted from the SARS-COV-2 survivors may be a promising approach for the protection of COVID-19 patients with antibody deficiency before the development of an effective vaccine [44].

However, the data about the potency of CPT in COVID-19 patients with primary and secondary humoral immunodeficiency is limited and has not been fully established, there are some case studies that have reported its proper effectiveness. For example, Clark et al. reported a 76-year-old COVID-19 case with lymphoma who was treated with a combination of bendamustine and rituximab that could lead to the impairment of humoral and cellular responses. After the failure of different treatment protocols against SARS-COV-2, the administration of hyperimmune plasma resulted in a rapid recovery in this patient [45]. In another report, an immunosuppressed COVID-19 patient with myeloid malignancy, disseminated tuberculosis, and kidney disease, was successfully treated after transfusion of CP and tocilizumab [46]. Furthermore, Mira et al. reported a primary antibody immunodeficient (x-linked agammaglobulinemia) male patient with COVID-19, whose health condition was improved following CP administration [47].

Presently, several clinical trials investigating the usage of CPT in COVID-19 are ongoing (as recorded in https://clinicaltrials.gov/), a number of which are summarized in Table 1. The trials are selected according to the recruitment status of the study (recruitment or completed state), age (18 years and older), and severity of symptoms in participants (admitted to the hospital or ICU with severe symptoms). Several other publications have discussed the usage of CPT in COVID-19 [32,33,35], thus more details would not be addressed here.

All in all, CPT has demonstrated acceptable safety, and it currently

Table 1
Summary of some clinical trials on CPT)recorded in https://clinicaltrials.gov/ at 6 June 2020).

No	Status	Estimated participants	Volume of administration	Outcome measurement	Time of transfusion	Study phase	Identifier
1	Recruiting	100	1 unit single dose	Changes in respiratory status after CP* transfusion/ Length of ICU and hospital stay/ Development of plasma transfusion reactions and immune complex disorders at days 1, 3, 7, and 28/ Change in anti CoV-2 IgM and IgG levels at days 1, 3, 7, and 28	Within 21 days of symptoms onset	Early phase I	NCT04412486
2	Recruiting	60	1–2 units on days 0, 3, 6 (Based on the availability of plasma)	Feasibility of administering CP to patients in the ICU who intubated and mechanically ventilated/ Overall survival of patients in the ICU receiving at least once dose of CP	–	Early phase I	NCT04353206
3	Recruiting	100	500 ml IV single dose	Mortality/ Requirement for and duration of mechanical ventilation/ Adverse events	–	Early phase I	NCT04355897
4	Recruiting	90	1–2 units on days 0, 2, 4, 6, and 8 (based on plasma availability)	Ventilation free days/ Mortality/ Duration of hospital and ICU stay	–	I	NCT04411602
5	Recruiting	20	250 ml on days 0 and 1	Adverse events/ Heart Failure, Pulmonary Edema, Allergic Reaction during CP transfusion or after it/ Viral load of SARS-CoV-2	–	I	NCT04333355
6	Recruiting	80	2 units single dose	Adverse events/Severity of symptoms/ Clinical status assessment/ Time to discharge/ Oxygen-free days/ Days of non-invasive ventilation/ Duration of hospitalization/ Mortality/ Changes in WBC with differential/ Changes in hemoglobin, platelets, creatinine, glucose, bilirubin, ALT, AST, PT measurement	–	I	NCT04397757
7	Recruiting	10	100 ml on day 0, 3, and 6	Change of INR, CRP, Oxygenation Index (OI) and Chest X-ray compared to pre and post transfusion/ Severe adverse events	–	I	NCT04407208
8	Recruiting	50	200 ml CP daily until SARS-CoV-2 is no longer detectable in the blood up to a maximum of 7 infusions	Duration of ventilation or oxygen therapy/ Adverse events related to CP/ Dose of plasma needed to clear viremia/ SARS-CoV-2 RNA detection by PCR in blood or serum/Duration of symptoms/ Inflammatory parameters/ Antibody response to SARS-CoV-2	–	I-II	NCT04384497
9	Recruiting	131	1–2 units (200–400) ml single IV infusion	Overall mortality and length of admission	Within 21 days of symptoms onset	II	NCT04354831
10	Recruiting	10	200 ml single dose	Overall survival/ Adverse events/ Lung injury	–	II	NCT04357106
11	Completed	29	200 to 600 ml according to the patient requirement	Proportion of patients remaining free of mechanical ventilation/ Mortality/Duration of hospital and ICU stay/ Improvement of respiratory status/ Requirements of Vasopressor		II	NCT04346446
12	Recruiting	120	2 units of 200–220 ml. In the absence of acute adverse events in the first 3 patients, an additional 2 units will be transfused 1 day after first 2 units: a total of 4 units / patient.	Severe adverse events/ Overall survival/ Time to discharge/ Oxygen-free days	Within 10 days of symptoms onset	II	NCT04345991
13	Recruiting	100	1–2 units (200–600 ml)	Number and type of adverse events/ Duration of hospital and ICU stay and intubation/Survival rate/ Changes in complete blood count, CRP*, fibrinogen, PT*, PTT* and BMP* in patients after receiving CP at day 0 and 7 (or the day of hospital discharge)	–	II	NCT04389710
14	Recruiting	30	200 ml single dose over 3 h	Improvement in respiratory disease/ Radiographic improvement/ Tolerability of CP/ Length of stay in hospital or ICU/ Duration of ventilation	–	II	NCT04385199
15	Recruiting	30	200 ml day 1 and 2 only if worsening of respiratory function or persistence of COVID symptoms for greater than 7 days after enrolment	Percentage and duration of mechanical Ventilation/ Hospitalization longer than 14 days or death during hospitalization/ Duration of fever/ length of ICU stay and admission/ Re-admission rate/ Length of viral clearance	Within 7 days of symptoms onset	II	NCT04375098
16	Recruiting	40	10–15 ml/kg at least once and if possible, daily for up to five sessions	Duration of mechanical Ventilation/ Mortality/ Adverse events/ Length of stay in ICU/ Days to clinical recovery		II	NCT04347681
17	Recruiting	126	200 ml single dose	Need of invasive mechanical ventilation/ Mortality rates/ Time to virologic cure/ Adverse events/ Length of stay in hospital	–	II	NCT04393727
18	Recruiting	200	–	Mortality rate: Significant reduction ($P < 0.05$) in mortality Lymphocytes: Significant increase ($P < 0.05$) in lymphocyte levels after 7 and 14 days after treatment Antibody levels and clinical improvement Significant correlation ($P < 0.05$) between hyperimmune plasma antibody levels and clinical improvement time	–	II-III	NCT04385043

(*continued on next page*)

Table 1 (*continued*)

No	Status	Estimated participants	Volume of administration	Outcome measurement	Time of transfusion	Study phase	Identifier
19	Recruiting	426	300 ml single IV infusion	Inflammatory cytokines Significant reduction (P < 0.05) of plasma levels of IL-6 and TNF-alpha 7 and 14 days after treatment initiation Overall mortality/ Duration of symptoms/ Length of stay in ICU and hospital/ Duration of oxygen therapy/ Duration of SARS-CoV-2 shedding from airways (airway samples will be taken on day 1–3-5–7-10–14, and at discharge)/Safety of plasma therapy	–	II-III	NCT04342182
20	Recruiting	500	Plasma will be administered at a rate of 500 ml/h	Mortality/ Hospitalization status/ Oxygen and ventilator free days/ Vasopressor-free days/ Hospital and ICU free days/ Adverse events	–	III	NCT04362176

*CP = convalescent plasma.
*CRP = C-reactive protein.
*PT = prothrombin time.
*PTT = partial thromboplastin time.
*BMP = Basic Metabolic Panel. Tests include measures of glucose, calcium, sodium, potassium, bicarbonate, chloride, blood urea nitrogen, and creatinine.

seems a promising choice for treating severe COVID-19 patients besides other therapeutic strategies [48].

6.1.1. Advantage and disadvantages of CPT

The previous experiences and efficacy in other similar diseases, as well as its feasibility, are the important advantages of CPT. Moreover, according to different reports, CPT is well-tolerated by receivers [35], but as all treatment approaches, this method may have some minor adverse effects as well. Generally, the most common adverse effects of CPT is related to transfusion events, such as chills, fever, rash, allergic reactions, circulatory overload, and hemolysis [40,49].

Additionally, several other problems are attributed to the mentioned approach, including lack of plasma donors, risk of cross-contamination, inconsistency from batch to batch, non-scalability, and the possibility of host reaction [50]. These pitfalls behoove pharmaceutical companies to manufacture polyclonal or monoclonal antibodies.

6.2. Antibodies

6.2.1. Targets of monoclonal antibodies against SARS-CoV-2

Different steps involved in the pathogenesis of SARS-CoV-2 can be targeted via antibodies. Our data in regards to the designing of an antibody against SARS-CoV-2 highly rely on the previous studies concerning SARS-CoV, the virus that is very similar to SARS-CoV-2. It has been shown that SARS-CoV-2 shares 89.1% and 50% nucleotide sequence identity with SARS-CoV and MERS-CoV, respectively [51,52]. Hence, in this review, only SARS-CoV-related data about the pathogenesis and the design of monoclonal antibody are included.

Monoclonal antibodies designed against SARS-CoV-2 can be categorized in three main groups based on their target: 1) antibodies that inhibit the virus attachment and entry by either targeting the virus structure or host receptors, 2) antibodies that interfere with the virus replication and transcription, 3) antibodies that hinder various steps of the immune system response. The schematic targets of monoclonal antibodies against SARS-CoV-2 are depicted in Fig. 2.

The first and most common targets are spike (S) proteins, which are located on the virus surface, generating its specific 'crown' shape [53]. SARS-CoV-2 starts its pathogenesis through the attachment of receptor-binding domain (RBD), located in the S1 subunit of the S protein, with ACE2. Thus, S proteins are considered as the most antigenic part of the virus with the main responsibility for the host immune responses [54]. It has been widely suggested that the previously-experimented SARS-CoV RBD neutralizing antibodies can be repurposed for SARS-CoV-2 [1,55,56]. The cross-neutralization capacity of antibodies relies on the conservation of the particular residues that are essential for the formation of specific bonds between RBD and the antibody, between the two types of viruses. For instance, an analysis was performed to determine which of the previously-proposed monoclonal antibodies against SARS-CoV can also cross-neutralize SARS-CoV-2. In the mentioned study, the residues for the formation of a salt bridge and electrostatic interaction between the m396 antibody and RBD were conserved between SARS-CoV and SARS-CoV-2. By contrast, antibodies, including R80 and F26G19 failed to interact with SARS-CoV-2 RBD in a similar way they did with SARS-CoV RBD due to the differences in their residues [57]. Surprisingly, it was shown that F26G19 neutralized SARS-CoV-2 more potently than SARS-CoV through other interactions [51]. Studies including cryoelectron microscopy of SARS-CoV-2 spike and analysis of the protein–protein interactions of SARS-CoV-2 and ACE2 receptor with energy-based methods revealed the amino acids 319–591 of SARS-CoV-2 RBD as important residues; the latter study also introduced the linear and conformational epitopes within this region as antibody targets [54,58].

Though the RBD has been considered as the main target of interest, some neutralizing or blocking antibodies have been shown to recognize other epitopes, including domains in S1 subunit, S-ectodomain, HR1 and HR2 domains in the S2 subunit, nucleoprotein (NP), or envelope

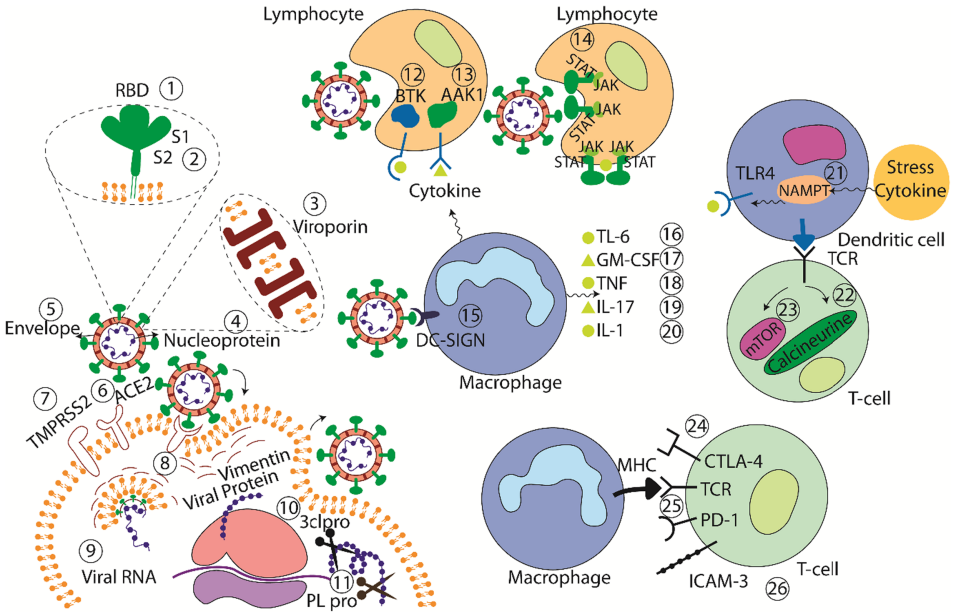

Fig. 2. Potential targets to curtail COVID-19. 26 potential targets for COVID-19 are depicted. 1) receptor binding domain (RBD) located in S1 protein, it is considered as the first and the main target for neutralizing antibodies, 2) S2 protein, consists of HR1 and HR2 domains, SARS-CoV neutralizing antibodies, including CR3022 and S309 potently cross-neutralize SARS-CoV-2 through binding with S2 protein, 3) viroporin, ion channel proteins, hypothesized to be targeted by dewetting monoclonal antibodies, 4) nucleoprotein, target of neutralizing antibodies, 5) envelope, target of neutralizing antibodies, 6) ACE2, angiotensin converting enzyme receptor 2, a receptor found on the cells of respiratory system, gastrointestinal tract, and endothelium, strongly binds with the virus spike, some monoclonal antibodies are designed to compete with the virus in attachment to the ACE2 receptor, 7) TMPRSS2, it is responsible for spike protein cleavage and viral entry, targeted by TMPRSS2 inhibitors including nafamostat and camostat mesylate 8) vimentin, cytoskeleton protein that is important in the formation of SARS-CoV-2-ACE2 complex, 9) viral RNA, 10) cysteine-like protease (3clPro), one of the important viral proteases and targets of antiviral drugs, 11) Papain-like proteases (PLpro), another important viral protease and target of antiviral drugs 12) Bruton tyrosine kinase (BTK), BTK inhibitors, including acalabrutinib, modulate cytokine storm in COVID-19 patients, 13) AP2-associated protein kinase 1 (AAK1), regulates viral endocytosis and is the target of immunomodulators, 14) signal transducer and activator of transcription proteins/Janusassociated kinase (STAT/JAK), modulates viral entry and cytokine storm, JAK inhibitors, including baricitinib are repurposed for SARS-CoV-2 inhibition, 15) dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN), mediates viral entry and is the target of human monoclonal antibody, 16) IL-6, one of the most important cytokines that activates downstream inflammatory process and causes acute respiratory distress syndrome, inhibited by different monoclonal antibodies, including Tocilizumab, 17) granulocyte–macrophage colony-stimulating factor (GM-CSF), causes positive feedback in inflammatory mediators and acute respiratory distress syndrome, target of monoclonal antibodies, 18) TNF, inflammatory mediator and cause of acute respiratory distress syndrome, target of monoclonal antibodies and TNF blockers, including etanercept, 19) IL-17, responsible for aggravation of cytokine storm and pulmonary edema and target of secukinumab, 20) IL-1, responsible for aggravation of cytokine storm and pulmonary edema, target of canakinumab, 21) nicotinamide phosphoribosyltransferase (NAMPT), upregulated by physical stress and causes an increase in the number of TLR4 and lung inflammation, target of monoclonal antibodies, 22) calcineurin, calcineurin inhibitors, including tacrolimus, block T-cell activation, 23) mTOR, mTOR inhibitors including sirolimus, inhibit memory B-cell activation and the antibody-dependent enhancement mechanism, 24) CTLA-4, immune check point and negative regulator of T-cell, target of monoclonal antibodies, 25) PD-1, immune check point and negative regulator of T-cell, target of monoclonal antibodies, 26) intercellular adhesion molecule 3 (ICAM-3), mediates the viral entry.

(E) protein [59–61]. For example, CR3022 cross-neutralized SARS-CoV-2 more strongly than other neutralizing antibodies against SARS-CoV, while it did not compete with ACE2 for binding to SARS-CoV-2. This observation indicates that CR3022 neutralizes SARS-CoV-2 through binding epitopes other than RBD [57]. Another study showed that the HR2 domain with an identity of 93% is highly conserved between SARS-CoV and SARS-CoV- 2, and thus neutralizing antibodies that target the HR2 domain, including 2B2, 1A9, 4B12, and 1G10 potently cross-neutralized SARS-CoV-2 [62]. Similarly, the S309 monoclonal antibody, retrieved from convalescent SARS-CoV patients, potently neutralized SARS-CoV-2 through a highly conserved domain distinct from RBD and did not interfere with the binding of S protein with the ACE2 receptor [63]. Moreover, in contrast to the above-mentioned importance of RBD in designing monoclonal antibodies, some studies have revealed the antibody-dependent enhancement of viral entry when the monoclonal antibody targets the RBD. It was shown that the binding of monoclonal antibody to the RBD triggers conformational changes that are similar to the alterations made following the binding of viral receptors to the viral RBD; hence, the binding mediates the virus entry to the cell via viral receptor-dependent pathways. However, as stated in the mentioned study, this mechanism depends on the monoclonal antibody dosage, expression of particular viral receptors (e.g. Fc receptors), and particular features of the monoclonal antibody [64]. Although ACE2 has been introduced as the main receptor of SARS-CoV, it may not be sufficient for the interaction between the cell and the virus. Other cellular factors, such as vimentin, a cytoskeleton protein, were revealed to be important in the formation of the ACE2-SARS-CoV complex [65]. Therefore, surface vimentin was recognized as a potential target for SARS-CoV. DS-SIGN/CD209 is also a transmembrane adhesion molecule, which is mainly expressed on interstitial dendritic cells and lung alveolar macrophages. It was shown that DS-SIGN also mediates the entry of SARS-CoV. A humanized monoclonal antibody was produced to interfere with the interaction of DS-SIGN and intercellular adhesion molecule 3 (ICAM-3), and thus inhibit SARS-CoV entry to the cell [66]. Similar proteins may be identified in regards to SARS-CoV-2.

In addition to inhibiting the virus entry, antibodies can intrude into the biological activities of the virus thereby preventing its replication. Fully human antibodies, which are capable of traversing across the cell membrane of infected cells and preventing virus replication, were made against several kinds of viruses, including influenza, hepatitis C virus, and Ebola [67]. Papain-like proteases (PLpro), cysteine-like protease (3CLpro), and other non-structural proteins (nsps) can be suggested as targets of interests that hinder SARS-CoV-2 replication [1,68].

Besides structural parts of the virus, various steps associated with the innate and the adaptive immune responses have been proposed as the most important targets of interest. For instance, the significant rise in the level of chemokines and cytokines, including IL-1β, IFN-γ, IP-10, and MCP-1, which is called the cytokine storm, can be inhibited by antibodies [69]. The preliminary studies of critically ill COVID-19 patients have shown that IL-6 may cause severe inflammatory responses that lead to acute respiratory distress syndrome [70]. Herein, tocilizumab, an IL-6 inhibitor monoclonal antibody, has gained significant attention. In a 21-patient clinical study recruited in China, tocilizumab resulted in the reduction of oxygen need in 75% of patients, lung lesion opacity absorption in 90.5% of patients, and correction of lymphocyte and C-reactive protein levels [70]. The significance of tocilizumab can be better explained since a noticeable number of 46 clinical trials

regarding its use against SARS-CoV-2 related pneumonia and respiratory tract infections were recorded in NIH until May 27, 2020. An increase in the level of some of these pro-inflammatory cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) results in a positive feedback in the number of other inflammatory mediators, including IL6, IL-23, and TNF. GM-CSF along with IL6 and IL23 also induce Th1/Th17 differentiation and the polarization of macrophages to M1 phenotypes, which in turn boost the inflammatory responses [71]. Th17 immune response also can aggravate the cytokine storm by raising the level of IL17, GM-CSF, IL21, and IL22 [72]. High levels of GM-CSF and Th17 cells were observed in the plasma of severe- to critically ill COVID-19 patients [73,74]. Herein, harnessing the upregulation of GM-CSF can prevent a cascade of inflammatory responses, which result in acute respiratory syndrome. Since monoclonal antibodies targeting one inflammatory mediator, may fail to control the whole cytokine storm and prevent the lung injury induced by acute respiratory distress syndrome, a newer approach to prevent lung injury was proposed. It was shown that physical stress such as excessive mechanical stress caused by ventilators upregulates the expression of a gene, called nicotinamide phosphoribosyltransferase (NAMPT). As the bioavailability of NAMPT increases, Toll-like receptor 4 (TLR4), which is responsible for lung inflammation, gets activated [75,76]. Herein, neutralization of circulating NAMPT by monoclonal antibodies can be another viable approach in preventing the lung injury caused by SARS-CoV-2.

In addition to the role of inflammatory mediators, understanding the adaptive immune responses helps us to repurpose or invent immunomodulatory antibodies to defeat SARS-CoV-2. For example, CD4+ and CD8+ T-cells are expected to promote the proliferation of neutralizing antibodies and the destruction of infected cells, respectively. However, lymphocytopenia is identified to play a role in the pathogenesis of severely-ill COVID-19 patients [77], which can be prevented or restored by regulating lymphocyte proliferation and apoptosis [78]. Herein, some studies have shown that sepsis may occur secondary to inflammatory responses. The immune imbalance, which occurs in sepsis, maybe as a result of T-cell depletion. PD-1 and CTLA-4 receptors are immune checkpoints that are expressed on the surface of T-cells and play a role as the negative regulator of T-cell function. Therefore, inhibiting the immune checkpoints by monoclonal antibodies is also an intriguing approach in defeating SARS-CoV-2 [79]. Furthermore, CD4+ cells express a receptor called c-chemokine receptor 5 (CCR5), which was established as a way of HIV entry to the cell [80]. This receptor could also be a potential target for SARS-CoV-2.

The level of different immunoglobulins is raised in response to SARS-CoV-2. Even though an increase in the level of immunoglobulins is attributed to pose neutralizing effect on SARS-CoV-2, a rise in anti-S IgG is associated with lung failure [81,82]. Complement systems also play a role in conferring both humoral and natural immunity; however, they have been also attributed to the refractory inflammatory diseases. Herein, C5a and C5a receptor, the members of the complement system, have been successfully targeted in different clinical trials of inflammatory diseases and thus can be recognized as possible targets in new diseases such as COVID-19 [83]. Additionally, TLR3, CD16, immunoreceptor tyrosin-based activation motif (ITAM), G-CSF, monocyte chemoattractant protein 1 (MCP1), TNFα, IL4, and IL10 are the other members of the immune system for which anti-SARS-CoV monoclonal antibodies were patented. These monoclonal antibodies could be re-evaluated for SARS-CoV-2 [84].

Besides the main strategies described above for designing monoclonal antibodies against SARS-CoV-2, some more novel approaches with a completely different mechanism were suggested. One of these strategies is using dewetting monoclonal antibodies. Dewetting transition is a process in which hydrophobic pores of the ion channels inhibit water transmission and thus impair the cellular performance. This phenomenon can be deployed to block viruses, bacteria, and autoimmune activities. Dewetting monoclonal antibodies are antibodies with a lipophilic fragment that target the transmembrane receptors and hinder the physiological water flow inside the channel. Such antibodies were produced against the influenza virus [85,86]. Recently, viroporins were identified in SARS-CoV-2, the ion channel proteins that are generated by the virus E protein and are responsible for different parts of the virus life cycle, including virus entry, assembly, release, and the whole pathogenesis cycle [87]. As suggested, dewetting monoclonal antibodies could be developed against SARS-CoV-2 viroporins and administered through the nose. These antibodies can deactivate the virus by targeting viroporins even before the virus will be able to bind to the host cells [88].

6.2.2. Design and production of monoclonal antibodies against SARS-CoV-2

Generally speaking, the antibodies could be usually produced at large-scale, either as monoclonal or polyclonal antibodies, using hybridoma cell-lines, animals, or cell-free protein synthesis [89]. Monoclonal antibodies can be produced via several technologies, including the production of high-affinity human antibodies in immunized transgenic mice (e.g. XenoMouse® or HuMAB® mice), various phage-display systems such as generating antibodies from immunoglobulin cDNA libraries in bacteria or mammalian cells, and obtaining memory B cells of convalescent patients that are immortalized by EBV transformation. All of these techniques were previously recruited to produce monoclonal antibodies against SARS-CoV [90]. The production of monoclonal antibodies against SARS-CoV-2 is in its incipient phase. Currently, our data about SARS-CoV-2 antibodies greatly comes from the studies in which the antibodies derived from the plasma of convalescent patients were analyzed. A recent study of the convalescent patients' antibodies demonstrated that anti-SARS-CoV-2 antibodies were versatile among the convalescent patients and each patient represented a unique pattern of antibody biodistribution. These results explain why it may be difficult to design specific anti-SARS-CoV-2 antibodies [91]. Therefore, the introduced antibodies in this study were mainly tested against SARS-CoV or approved for other immune inflammatory diseases such as rheumatoid arthritis, cancers, and other viral infections. An extra method for designing antibodies against SARS-CoV-2 can be based on the antibody-antigen computational simulation [51]. For instance, an online docking server using the CoDockPP engine is constructed to predict the docking modes between antibodies or other peptides. This server is freely available at http://ncov.schanglab.org.cn. Identified structural parts of SARS-CoV-2 and the homologous parts of other coronaviruses were gathered to produce the mentioned docking server [92].

6.2.3. Examples of monoclonal antibodies

The antibodies retrieved from the previous studies on SARS-CoV or computational studies concerning SARS-CoV-2, which mainly target the virus structure or host receptors are shown in Table 2. Despite a great homology between SARS-CoV and SARS-CoV-2, the cross-reactivity of SARS-CoV antibodies against SARS-CoV-2 is still under debate. For instance, some highly-conserved regions are found in SARS-CoV-2, which are absent in SARS-CoV. The c-terminal of SARS-CoV-2 RBD highly differs from that of SARS-CoV. Moreover, an extra furin cleavage site was found between S1 and S2 subunits in SARS-CoV-2, which is absent in SARS-CoV. These differences may not affect the ability of both viruses in interacting with the ACE2 receptor but explain the different levels of affinity among neutralizing antibodies with the two viruses [51,57,93,94]. Moreover, a recent study revealed that the antibodies targeting RBD of the coronavirus family are virus species-specific, while those that target viral parts outside RBD are capable of cross recognition [91]. In an antibody epitope computational analysis, it was revealed that 85.3% of antibody epitopes in the SARS-CoV-2 spike were novel in comparison with those in SARS-CoV [95]. Therefore, antibodies suggested in Table 2 ought to be reevaluated to be used against SARS-CoV-2. Taken together, among the introduced monoclonal

Table 2
Monoclonal antibodies identified based on the previously studied SARS-CoV antibodies or computational studies.

Antibody	Mechanism of action	Identification method	Ref
80R	Competes with ACE2 for association with S1 domain	Screening phage display library	[96]
S3.1	Prevents the cytopathic effect of virus and viral entry by recognizing spike	Analysis of immune SARS-CoV patients' serum and *in vivo* study in mice	[60]
A group containing 20 neutralizing antibodies, including S101.1, S102.1, S103.3, S104.1, S105.2, S106.1, S107.4, S108.1, S109.2, S132.9, S128.5, S127.6, S124.4, S159.1, S160.1, S215.13, S216.9, S217.2, S218.6, S219.2	Neutralize spike by binding to residues 318–510		
A group containing five neutralizing antibodies, including S18.1, S20.1, S21.1, S23.4, S24.1	Neutralize nucleoprotein		
S5.1	Neutralizes envelope protein		
S13.1	Not defined		
CR3014	Blocks S1 domain	Screening phage display library	[97]
CR3022	Blocks S1 domain, neutralizes mutated SARS-CoV escape from CR3014, induces synergistic effect and dose reduction in combination with CR3014	Screening phage display library	[98]
	Higher affinity to SARS-CoV-2 S protein than SARS-CoV	Antibody-antigen docking simulation	[51]
	Neutralizes SARS-CoV and SARS-CoV-2 S protein by binding epitopes other than RBD	Cross neutralization determined by ELISA and BLI	[57]
m396	Competes with ACE2 for association with S1 domain Neutralizes SARS-CoV resistant against 80R and S3.1 antibody Neutralizes all zoonotic SARS-CoV except bat-originated ones	Screening phage display library	[99]
S230.15	Competes with ACE2 for association with S1 domain		
S230	Mimics receptor attachment and promotes conformational rearrangement of S protein	Cryoelectron microscopy study of S protein in combination with antibody	[100]
B1	Neutralizes S2 epitope	Screening phage display library	[101]
A group containing 27 human monoclonal antibodies	Neutralizes S1 domain by binding to residues 318–510 within RBD or 12–261 located at the upstream of RBD; antibodies targeted RBDs were the most reactive ones	Screening human monoclonal antibodies produced in XenoMouse® against SARS-CoV S protein	[61]
A group containing 57 human monoclonal antibodies	Neutralizes S2 domain		
201	Neutralizes S1 domain by binding to residues 490–510; provides complete protection against SARS-CoV infection in murine model	Screening human monoclonal antibodies produced in HuMAB mice® against SARS-CoV S protein	[102]
68	Neutralizes S1 domain by binding to residues 130–150; provides complete protection against SARS-CoV infection in murine model		
A group containing nine human monoclonal antibodies, including 1F8, 4A4, 1D12, 2A12, 5C3, 2B12, 6H2, 6C9, and 4F9	Neutralize HR1 domain	Screening human monoclonal antibodies produced in XenoMouse® against SARS-CoV S protein	[59]
A group containing 13 human monoclonal antibodies, including 5G8, 5B10, 3A11, 5E9, 6H1, 1E10, 3H11, 5B9, 5D7, 2D2, 3E10, 5G9, and 2D6	Neutralize HR2 domain		
A group containing 17 human monoclonal antibodies, including 1F1, 3F1, 4E11, 6C5, 4G10, 3F9, 6D8, 2C6, 2G11, 1D11, 4E6, 1C1, 2B9, 2E11, 1G12, 6H6, and 1D5	Neutralize S-ectodomain domain		
F26G19	Antibody that binds to SARS-CoV RBD and blocks the contact of virus with ACE2 receptors	Studying x-ray crystal structure of Fab of mouse monoclonal antibody in complex with SARS-CoV RBD	[103]
	Higher affinity to SARS-CoV-2 S protein than SARS-CoV	Antibody-antigen docking simulation	[51]
F26G15	Neutralizes nucleoprotein	Screening murine monoclonal antibodies by enzyme immunoassays	[104]
F26G1, F26G6, F26G8, F26G18, F26G19	Neutralize spike		
A group containing 8 antibodies, including five mutated forms of the antibody with the PDB ID of 2GHW and three mutated forms of the antibody with the PDB ID of 6NB6	Neutralize spike protein	Analysis of 1933 antibody against SARS-CoV-2 via machine learning, neutralization was identified based on neutralizing scaffold of 80R antibody	[105]
1C6, 1H1, 6B9, 4B12, 1G10	Interfere with the HR1 and HR2 interaction and inhibit the membrane fusion and virus entry	Monoclonal antibodies generated in immunized mice against S fragment were analyzed by immunoassays	[106]
2B2,2G2, 1A9	Occupy the upstream of HR2 domain and cause steric hindrance		
256	Neutralizes virus by enhancing binding of S protein to the surface of target cell	Identified in scFv libraries	[107]
4D4	Binds to the N-terminal of RBD and inhibits post binding steps	Screening human monoclonal antibodies produced in XenoMouse® against SARS-CoV S protein	[108]
47D11	Cross-neutralizes S1 subunit of SARS-CoV and SARS-CoV-2	Derived from immunized transgenic H2L2 mice and cross-reactivity identified by ELISA	[109]
1A9, 2B2, 4B12, 1G10	Neutralize HR2 domain	Murine monoclonal antibodies generated using S protein fragment and neutralization capacity identified by immunoassay	[62]

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Table 2 (*continued*)

Antibody	Mechanism of action	Identification method	Ref
Dewetting monoclonal antibodies	Dewetting viroporin of SARS-CoV-2	Hypothesized based on dewetting transition phenomenon	[88]
P2C-1F11, P2B-2F6, P2C-1A3	Block RBD	Antibodies derived from convalescent patients and tested via immune assays	[91]
S309, S306	Neutralize S protein through glycan containing epitope distinct from RBD, does not compete with receptor attachment Induce NK-mediated antibody-dependent cell cytotoxicity	Identified from memory B-cell of SARS-CoV patients	[63]
B38 and H4	Have synergistic action in binding with RBD and neutralizing the virus, their synergistic action avoids immune escape	Isolated from SARS-CoV-2 convalescent patients	[110]

antibodies in these study, F26G19, CR3022, and 47D11 were shown to cross-neutralize SARS-CoV and SARS-CoV-2.

Further information in this study concerning monoclonal antibody data against SARS-CoV-2 was retrieved from clinical trial data recorded in clinicaltrials.gov or biotechnology and pharmaceutical companies' websites, which are summarized in Tables 3 and 4, respectively. Monoclonal antibodies, which are proposed to date against SARS-CoV-2, mainly target immune responses rather than the virus structure. Various inclusion and exclusion criteria were considered in clinical trials as it is stated in clinicaltrials.gov. Most of the clinical trials were indicated for severe to critically COVID-19 patients with progressed pneumonia. However, one clinical trial related to tocilizumab, being held in the University of Chicago (NCT04331795), aims to prevent clinical decompensation in the hospitalized non-critically ill patients. Some of the trials aim to assess the efficacy of monoclonal antibodies alone, while others are administered in combination with other medications. For example, in one study in Spain (NCT04332094), tocilizumab is administered with hydroxychloroquine and azithromycin. Moreover, studies evaluate the efficacy of a medication alone or in comparison with other treatment options, including a study in China (NCT04306705) in which tocilizumab is compared with continuous renal replacement therapy. In some clinical trials, such as the one related to thymosin, lymphocytopenia was an eligibility criterion along with severe pneumonia. Different primary and secondary endpoints were considered in clinical trials, among them a reduction in fever and decreased need to oxygen can be mentioned. Pharmaceutical companies have proposed various kinds of monoclonal antibodies against SARS-CoV-2, details of which are explained in Table 4. Many of the proposed antibodies target immune system responses, including GM-CSF, IL-1β, IL-17, C5a, and NAMPT, while some others, developed by Eli Lilly and AbCellera, Vir Biotechnology, Adaptive, Amgen, and Harbour Biomed, are designed to neutralize SARS-CoV-2 structure. However, the mechanisms and specificities of the latter antibodies have not been elaborated to date and thus should be followed in companies' websites.

6.2.4. Polyclonal antibodies against SARS-CoV-2

For effective passive immunotherapy, several epitopes ought to be targeted rather than one epitope. Moreover, the design of monoclonal antibodies and their testing at a clinical stage is a long pathway followed by the fact that the massive production of monoclonal antibodies might be costly, time-consuming, and labor-intensive; factors that cannot be underestimated in the time of a pandemic outbreak and an urgent need to effective therapeutics. Herein, the administration of a cocktail of monoclonal antibodies or multivalent antibodies for the neutralization of SARS-CoV-2 also seems more rational [130]. For example, Regeneron Pharmaceuticals proposed the use of a cocktail of the neutralizing antibodies derived from a genetically engineered mouse to fight with SARS-CoV-2. Three other pharmaceutical companies, including GigaGen, Emergent BioSolution, and SAB Biotherapeutics also have developed polyclonal antibodies against SARS-CoV-2, called rCIG, COVID-EIG/HIG, and SAB, respectively (Table 4). Polyclonal antibodies produced by immunized animals or a particular cell line technology are expected to mimic convalescent plasma therapy with a higher potency than their plasma-derived equivalents as well as better clinical outcomes. Furthermore, the risk of contamination and host reactions will be reduced compared with their plasma equivalents; dosing and kinetics also would be more predictable and scalable. Moreover, targeting more than one epitope can cause synergistic effects in neutralization and would limit the formation of escape-mutants. For instance, a recent study revealed that a cocktail of antibody noticeably enhanced SARS-CoV-2 neutralization compared with the use of one monoclonal antibody [63].

6.3. Immunomodulators

Several classes of immunomodulators including tyrosine kinase inhibitors, mTOR inhibitors, calcineurin inhibitors, antimetabolites, TNF blockers, metal-based agents, and other anti-inflammatory agents might be of value in the treatment of COVID-19. Janus-associated kinase (JAK) inhibitors are of high interest among the mentioned immunomodulators.

6.3.1. JAK inhibitors

Although ACE2 receptors have been recognized as the main receptors for the entry of SARS-CoV-2, it was shown that SARS-CoV-2 also attacks the cells that do not have ACE2 receptors, including lymphocytes. It is proposed that SARS-CoV-2 may also enter the cell through clathrin-mediated endocytosis, thus it can be defeated through inhibiting endocytosis. Members of numb-associated kinase (NAK) family including AP2-associated protein kinase 1 (AAK1) and Janus-associated kinase (JAK) are two of the main regulators of endocytosis, which can be inhibited and suggested as a possible target for controlling different viral infections such as SARS-CoV-2 infection [131]. JAK inhibitors include ruxolitinib, baricitinib, fedratinib, upadacitinib, tofacitinib, and filgotinib, which are mainly used for the treatment of myelofibrosis or other inflammatory diseases, including rheumatoid arthritis, ulcerative colitis, and psoriasis. Myelofibrosis is a blood cancer in which chronic leukemia is observed. Lymphocytopenia notably occurs in COVID-19 patients as well and is considered as one of the major markers of the disease. Hence, it seems logical to repurpose JAK inhibitors in COVID-19 patients, since the disease mimics the symptoms that occur in myelofibrosis. Moreover, JAK inhibitors with their high anti-inflammatory properties can curtail the cytokine storm that happens in COVID-19 patients. It is of special notice that the use of JAK inhibitors for the prevention of SARS-CoV-2 may be a double-edged sword. For instance, although JAK inhibitors are considered as relatively safe therapeutics for SARS-CoV-2, they may inhibit inflammatory mediators, such as INF-α, which play a vital role in the immune responses and thwarting SARS-CoV-2 [132]. In fact, broad immunosuppression either by JAK inhibitors or other immunosuppressants may delay the virus clearance and perpetuate the illness. The possible benefits of

Table 3
Clinical trials of monoclonal antibodies against SARS-CoV-2 recorded in clinicaltrials.gov.

Antibody name	Mechanism	Sponsor	Clinical trial identifier	Start-end	Participants number	Study location	Study protocol
Sarilumab (Kevzara®) (REGN88) (SAR153191)	Anti-IL-6 receptor	Regeneron & Sanofi	NCT04315298	Mar 2020-Mar 2021	400	Global (63 study locations)	Single IV low & high dose
		Lisa Barrett Nova Scotia Health Authority Dalhousie University	NCT04321993	Mar 2020-Feb 2021	1000	–	200 mg single SQ dose
Tocilizumab (TCZ) (Roactemra®) (Actemra®)	Anti-IL-6 receptor	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau Instituto de Salud Carlos III	NCT04332094	Apr 2020-Sep 2020	276	Spain	162 mg q12 h SQ (one day) + hydroxychloroquine + Azithromycin
		National Cancer Institute, Naples	NCT04317092	Mar 2020-Dec 2020	330	Global (27 study locations)	8 mg/kg (max 800 mg per dose) q 12 h
		University of Chicago	NCT04331795	Apr 2020-Jul 2020	50	USA	Single low dose (starting with 80 mg) or high dose (starting with 200 mg), repeat dose if needed
		University Hospital Inselspital, Berne Roche Pharma AG	NCT04335071	Apr 2020-Oct 2020	100	Switzerland	8 mg/kg (max 800 mg per dose), IV infusion; repeat dose if needed
		Hoffmann-La Roche	NCT04320615	Apr2020-Aug 2021	330	–	
		University of L'Aquila	NCT04332913	Apr 2020-Dec 2020	30	–	–
		Tongji Hospital	NCT04306705	Feb 2020-May 2020	120	China	8 mg/kg IV infusion
		Peking University First Hospital	NCT04310228	Mar 2020-May 2020	150	China	8 mg/kg (max 800 mg per dose) + favipiravir
		MedSIR	NCT04335305	Mar 2020-May 2020	24	–	Single dose of 8 mg/kg (max 800 mg per dose), IV infusion + pembrolizumab
		Centre Leon Berard	NCT04333914	Apr 2020-Jun 2020	273	France	Single dose 400 mg IV + nivolumab + chloroquine
		University Hospital, Ghent	NCT04330638	Apr 2020-Sep 2020	342	Belgium	Single dose of 8 mg/kg (max 800 mg per dose), IV infusion
		Marius Henriksen Lars Erik Kristensen	NCT04322773	Mar 2020-Jun 2021	200	Denmark	Single dose 400 mg IV
		Università Politecnica delle Marche	NCT04315480	Mar 2020-Apr 2020	30	Italy	Single IV dose of 8 mg/kg
		Assistance Publique - Hôpitaux de Paris	NCT04331808	Mar 2020-Mar 2021	240	–	IV dose of 8 mg/kg, repeat dose if needed
Siltuximab (Sylvant®)	Anti-IL-6	University Hospital, Ghent Belgium Health Care Knowledge Centre	NCT04330638	Apr 2020-Sep 2020	342	Belgium	Single dose of 11 mg/kg IV infusion + anakinra + tocilizumab
		Judit Pich Martínez	NCT04329650	Apr 2020-May 2020	100	Spain	Single dose of 11 mg/kg IV infusion
		A.O. Ospedale Papa Giovanni XXIII	NCT04322188	Mar 2020-May 2020	50	Italy	–
Bevacizumab (An ke da)	VEGF inhibitor	Qilu Hospital of Shandong University	NCT04305106	Mar 2020-Jun 2020	140	China	7.5 mg/kg IV
		Qilu Hospital of Shandong University Renmin Hospital of Wuhan University Moriggia-Pelascini Gravedona Hospital	NCT04275414	Feb 2020-Apr 2020	20	China	500 mg IV
Emapalumab (Gamifant®)	Anti-IFNγ	Swedish Orphan Biovitrum	NCT04324021	Mar 2020-Jul 2020	54	Italy	IV infusion every three days for a total of five infusions. Day 1: 6 mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + anakinra

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Table 3 (*continued*)

Antibody name	Mechanism	Sponsor	Clinical trial identifier	Start-end	Participants number	Study location	Study protocol
Thymosin	Anti-PD-1	Southeast University, China	NCT04268537	Feb 2020-Apr 2020	120	China	1.6 mg SQ, qd (for five days)
Pembrolizumab (MK-3475) (Keytruda®)		MedSIR	NCT04335305	Mar 2020-May 2020	24	–	Single dose of 200 mg IV infusion + tocilizumab
Nivolumab		Centre Leon Berard	NCT04333914	Apr 2020-Jun 2020	273	France	Single dose of 0.3 mg/kg IV infusion + tocilizumab + chloroquine
Eculizumab (Soliris®)	Distal complement inhibitor, preventing formation of the membrane attack complex	Hudson Medical	NCT04288713	–	–	–	–
Meplazumab	Anti -CD147	Tang-Du Hospital	NCT04275245	Feb 2020-Dec 2020	20	China	10 mg IV infusion, every two days

immunosuppressants should be assessed versus their potential to impair the immune system and cause bacterial infections as well [133].

JAK inhibitors are classified as JAK1, 2, or 3 inhibitors, and their inhibition is either exclusive (JAK2 inhibitor) or non-exclusive (JAK1/3, JAK1/2 inhibitor). Several *in vitro/ in vivo* or computational studies concerning various viral infections or SARS-CoV-2 were performed to assess the safety and efficacy of different JAK inhibitors and compare the advantage of one JAK inhibitor over another member of the family. For instance, JAK2 inhibitors, such as fedratinib, function more precisely in the control of cytokine storm. JAK2 inhibitors block the Th17 differentiation thereby reducing the level of IL-17, IL22, and GM-CSF, which are responsible for the aggravation of cytokine storm and pulmonary edema. Moreover, JAK2 inhibitors have a marginal effect on IL21, which is responsible for B cell function, and do not disrupt innate immune response, since the inhibition caused by JAK2 inhibitors is transient and reversible [72]. Another member of this family, baricitinib, is of special interest due to its advantages over other JAK inhibitors and has been highly studied. Baricitinib inhibits another regulator of endocytosis, called cyclin G associated kinase, through which it can defeat the viral infection [134]. Baricitinib has been also suggested as the best choice among other JAK inhibitors due to its acceptable profile of side effects, the possibility of once-daily dosing, higher potency, and advantageous pharmacokinetics. The inhibitory doses of baricitinib were well-tolerated by patients with inflammatory diseases in comparison with other kinase inhibitors [135,136]. Moreover, baricitinib represents low protein binding and minimal interaction with drug transporters or metabolic enzymes; thus, it is preferred over other JAK inhibitors for administration along with an anti-viral regimen [136]. In contrast to the above-mentioned benefits of baricitinib, some clinical studies suggested that baricitinib may not be an ideal option for the treatment of COVID-19 due to the possibility of causing lymphocytopenia, neutropenia, viral reactivation, and enhancement of coinfection [137]. Other JAK inhibitors, including upadacitinib and filgotinib, were also shown to impair interferon-mediated antiviral responses and perpetuate SARS-CoV-2 infection. Herein, the incidence of secondary viral infections, including herpes zoster was observed, which was shown to be more prevalent in immunocompromised patients. Hence, JAK inhibitors, particularly baricitinib, should be administered with meticulous consideration, especially in susceptible and immunocompromised patients [138]. Next, ruxolitinib was listed as one of the top hit compounds in an advanced bioinformatics analysis of available medications for SARS-CoV-2. The mentioned study aimed to identify compounds that counteract the expression of SARS-CoV-2-related genes [139]. To date, only three JAK inhibitors have entered clinical studies on COVID-19 patients, including baricitinib, ruxolitinib, and tofacitinib, among which many of the studies are related to baricitinib and ruxolitinib (Table 5).

6.3.2. Other tyrosine kinase inhibitors

Bruton tyrosine kinase (BTK) inhibitors are another group of tyrosine kinase inhibitors, which has been repurposed to modulate the cytokine storm ensuing COVID-19 infection. BTK signaling leads to B cell proliferation and activation of cytokine pathway. BTK inhibitors are mainly approved for the treatment of an aggressive form of B cell lymphoma, called mantle cell lymphoma. This group includes acalabrutinib, zanubrutinib, tirabrutinib, and ibrutinib, among which ibrutinib was shown to have less efficacy and more toxicity [140]. AstraZeneca® incorporation has designed a clinical trial to assess the efficacy of one of these BTK inhibitors, called acalabrutinib, to alleviate the cytokine storm of SARS-CoV-2 infection (Table 5). In addition to BTK inhibitors, other kinase inhibitors, including erlotinib and sunitinib were also shown to interfere in viral entry through inhibiting JAK and AAK1. However, they are not classified as JAK inhibitors and are not preferred over JAK inhibitors due to less efficacy and higher toxicity [135,136]. Sorafenib was also hypothesized to be repurposed in COVID-19 based on a drug-gene interaction analysis [141].

Table 4
Antibodies candidate against SARS-CoV-2 under investigation by pharmaceutical and biotechnology companies.

Antibody	Mechanism	Company	Stage of study/identification method	Ref
Gimsilumab	Anti GM-CSF monoclonal antibody	Roviant Sciences	In clinical stage for inflammation and rheumatic disease Prioritized in clinical trial for SARS-CoV-2	[111]
TJM2		I-MAB Biopharma	Phase 1 clinical trial completed and revealed favorable safety	[112]
Lenzilumab		Humanigen Inc.	Currently in clinical stage for leukemia and lymphoma	[113]
Canakinumab (Ilaris®)	IL-1β inhibitor	Novartis	In clinical stage for several inflammatory diseases including arthritis, periodic fever and lung cancer; Repurposed by Novartis for COVID-19	[114]
Secukinumab (Cosentyx®)	IL-17 inhibitor	Novartis	In clinical stage for several autoimmune diseases including psoriasis; repurpose by Novartis for COVID-19	[69]
Not mentioned	Binds to highly-conserved epitopes within SARS-CoV and SARS-CoV-2	Vir biotechnology with WuXi biologics and Biogen	Enters clinical trial within 3–5 months Aimed to confer short- and long-term immunity and use as prophylaxis	[115]
Not mentioned	Block virus RBD interaction with ACE2	Distributed Bio	Computational studies; Thousands of fully human high affinity monoclonal antibodies engineered by Tumbler and SuperHuman 2.0 technology	[116]
Not mentioned	Anti SARS-CoV-2	Eli Lilly and AbCellera	Experimental stage; screened functional antibodies of recovered COVID-19 patients	[117]
TZLS-501	Fully human monoclonal antibody targeting the receptor of IL-6, it binds to both membrane-bound and soluble forms of IL-6R, and rapidly depletes the circulating levels of IL-6 in blood.	Tiziana Life Sciences and Novimmune	Preclinical stage	[118]
ALT-100	Neutralize circulating NAMPT	Aqualung Therapeutics Corp.	Preclinical stage	[119]
Not mentioned	Fully human monoclonal antibody	Harbour Biomed; Mount Sinai Health System	Experimental stage Produced with the technology of H2L2 Harbour mice®	[120]
Pritumumab	Fully human IgG antibody targeting vimentin	Nascent Biotech Inc.	Received FDA approve for several carcinoma Research began for COVID-19	[121]
Leronlimab (PRO140)	Antagonizes CCR5 on T-cells and prevents viral entry	CytoDyn	A 10-patient clinical study against COVID-19 Initially developed against HIV; in clinical trial for HIV and breast cancer	[122]
BDB-1	Anti C5a	Beijing Defengrei Biotechnology	Beijing Defengrei Biotechnology passes the phase II of clinical trial	[123]
IFX-1		InflaRx	InflaRx received approval for starting the clinical trial in Netherlands	
Not mentioned	Fully human neutralizing antibodies targeting SARS-CoV-2	Adaptive and Amgen	Screening B cell receptors of patients recovered from COVID-19 to find neutralizing antibodies	[124]
VIR-7831/VIR-7832	Neutralize highly conserved epitope in s protein Induce NK-mediated antibody-dependent cell cytotoxicity	VIR biotechnology and GSK	Designed based on S309 (isolated from SARS-Cov patients)	[125]
SAB	Anti SARS-CoV-2 fully human poly clonal antibodies	SAB Biotherapeutics	Antibodies produced in genetically engineered cattle will enter clinical trial by early summer SAB-301 against MERS passes phase 1 of clinical trial and entered phase II/III	[126]
–	Target multiple viral S epitope	ImmunoPrecise	Using B cell Select® and Deep Display® technology	[127]
COVID-HIG and COVID-EIG	Hyperimmune polyclonal antibody derived from human plasma or immunized horse	Emergent BioSolutions	Enter clinical trial within 4–5 months	[128]
rCIG	Recombinant anti SARS-CoV-2 hyperimmune gammaglobulin, polyclonal antibodies	GigaGen	Preclinical stage Aimed for COVID19 hospitalized patients and prophylaxis in high risk individuals	[129]
Antibody cocktail including REGN3048-3051	Fully human multivalent antibodies against the spike protein isolated from genetically modified mice or recovered COVID-19 patients	Regeneron	Phase 1 clinical trial for MERS completed last year Clinical trial for SARS-CoV-2 starts by early summer	[130]

Table 5
Clinical studies on immunomodulators in COVID-19.

Immunomodulator	Mechanism	Sponsor	Clinical trial identifier	Start-end	Participant number	Study location	Administration
Baricitinib (Olumiant®)	JAK inhibitor	University of Colorado	NCT04340232	Apr 2020-Aug 2020	80	USA	2 mg PO
		Hospital Universitario de Fuenlabrada	NCT04346147	Apr 2020-Aug 2020	165	Spain	4 mg PO, QD + 200 mg BID Hydroxychloroquine
		Hospital of Prato	NCT04320277	Mar 2020-Apr 2020	60	Italy	4 mg PO, QD (2 weeks) + ritonavir 600 mg BID
		Thomas Benfield	NCT04345289	Apr 2020-Jun 2021	1500	Denmark	4 mg PO, QD (one week)
		Lisa Barrett Nova Scotia Health Authority Dalhousie University	NCT04321993	Apr 2020-Feb 2021	1000	Canada	2 mg PO, QD (10 days)
Tofacitinib	JAK 1/3 inhibitor	Università Politecnica delle Marche	NCT04332042	Apr 2020-Jun 2020	50	Italy	5 mg, BID (2 weeks)
Ruxolitinib (Jakafi®, Jakavi®)	JAK 1/2 inhibitor	University of Colorado, Denver	NCT04348071	Apr 2020-Aug 2020	80	USA	10 mg, BID (2 weeks)
		Grupo Cooperativo de Hemopatías Malignas	NCT04334044	Apr 2020-Jun 2020	20	Mexico	10 mg, BID (until observation of changes in pneumonia)
		University Health Network, Toronto	NCT04331665	Apr 2020-Oct 2020	64	Canada	10 mg, BID (two weeks) followed by 5 mg, BID (2 days) and 5 mg, QD (one day)
		Prof. Dr. med. Andreas Hochhaus	NCT04338958	May 2020-Jan 2021	200	Germany	10 mg, BID (7 days)
		Fundación de investigación HM Apices Soluciones S.L.	NCT04348695	Apr 2020-May 2020	94	Spain	10 mg, BID (seven days) + 40 mg simvastatin QD (2 weeks)
Acalabrutinib	BTK inhibitor	AstraZeneca Acerta Pharma B.V.	NCT04346199	Dec 2020-Jan 2020	428	–	PO
Tacrolimus (Advagraf®, Modigraf®)	Calcineurin inhibitor	Hospital Universitari de Bellvitge Institut d'Investigació Biomèdica de Bellvitge	NCT04341038	Apr 2020-Jun 2020	84	Spain	Necessary dose to obtain the blood level of 8–10 ng/ml + 120 mg methylprednisolone QD (3 consecutive days)
Sirolimus (rapamycin) (rapamune®)	mTOR inhibitor	University of Cincinnati	NCT04341675	Apr 2020-Jul 2020	30	USA	6 mg loading dose + 2 mg, QD (2 weeks)
Thalidomide (fanyingting®)	Anti-inflammatory, TNF-α inhibitor	Wenzhou Medical University	NCT04273529	Feb 2020-May 2020	100	–	100 mg, PO, QN, (2 weeks)
CD24Fc	Anti-inflammatory	OncoImmune, Inc.	NCT04317040	Apr 2020-May 2021	230	USA	480 mg, IV infusion, single dose
Fingolimod	Sphingosine-1-phosphate receptor regulators	Hospital of Fujian Medical University	NCT04280588	Feb 2020-Jul 2020	30	China	0.5 mg, PO, QD (3 days)

6.3.3. mTOR inhibitors

Another mechanism of immunosuppression, which has been proposed, is related to the use of mTOR inhibitors. The cytokine storm in COVID-19 patients is attributed to a mechanism, called antibody-dependent enhancement, in some systematic reviews [142]. This phenomenon happens when the virus triggers the production of cross-reactive antibodies by memory B cells. These cross-reactive antibodies enhance virus delivery to the macrophages and thus contribute to the massive replication of the virus without being captured by the immune system. mTOR inhibitors were found to inhibit the activation of memory B cell and prevent the antibody-dependent enhancement mechanism. mTOR inhibitors also were shown to inhibit the replication of MERS-CoV in the *in vitro* studies [142]. Some mTOR inhibitors, including rapamycin or sirolimus, were hypothesized to be repurposed in COVID-19 clinical studies. Sirolimus was shown to inhibit viral replication and release in patients with severe pneumonia and acute respiratory failure [143]. The computational analysis of protein–protein interactions and gene-enrichment network also suggested that sirolimus can be repurposed for SASR-CoV-2 [144]. Moreover, a clinical study of sirolimus on COVID-19 patients has been recently started (Table 5).

6.3.4. Antimetabolites

Papain-like protease (PLpro) is a viral protease responsible for coronavirus genome replication with deubiquitinating activity [145]. PLpro has been mainly the target of viral inhibitor class of medications. However, antimetabolites were also shown to be effective on PLpro due to their pharmacological action. For instance, 6-mercaptopurine (6MP) and 6-thioguanine (6TG) were shown to be the specific inhibitors of SARS-CoV PLpro [146]. Mycophenolate mofetil is another immunosuppressant that was shown to target PLpro in SARS-CoV and MERS-CoV in both *in vitro* and *in vivo* studies. However, further clinical studies are needed to assess its efficacy against SARS-CoV-2 [147]. There is no definitive evidence about the efficacy of other antimetabolites including methotrexate in COVID-19 patients [147].

6.3.5. Calcineurin inhibitors

Calcineurin inhibitors such as tacrolimus might be effective against SARS-CoV-2, since they inhibit calcineurin, thereby blocking T cell activation. Tacrolimus, which is mainly used in organ transplant, was shown to be effective against MERS-CoV in a renal transplant patient compared with a similar patient who did not receive tacrolimus as a part of the transplant regimen [148]. Tacrolimus was also found to be effective against SARS-CoV in a study on cell lines. However, further studies undoubtedly are required to assess its efficacy against SARS-CoV-2 [149]. There is no definitive evidence about the efficacy of other calcineurin inhibitors including cyclosporine [147].

6.3.6. Metal-based agents

Metal-based agents with different metal centers, including gold, ruthenium, and bismuth were suggested to be used in COVID-19 patients [150]. The gold compound, called auranofin (Ridaura®) is an FDA approved compound, which was initially proposed for rheumatoid arthritis. The exact mechanism of auranofin is still unclear; however, it is classified as an immunomodulatory and anti-inflammatory agent. In recent years, auranofin has gained attention in viral infections, including HIV. In the case of HIV, it was revealed to be more effective than hydroxychloroquine in control of viral production, latency, and viral reactivation [151]. It was also hypothesized that auranofin can interfere with IL-6 signaling by inhibiting JAK1 and STAT3 pathways [152]. It was shown that a low micromolar concentration of auranofin strongly inhibited SARS-CoV-2 viral replication and reduced the viral-induced cytokine expression in human cells [153].

6.3.7. TNF-α blockers and other anti-inflammatories

TNF-α was shown to be associated with SARS-CoV pulmonary injury; therefore, TNF-α blockers, which are mainly used in the treatment of autoimmune and inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis, can be suggested as a potential target for SARS-CoV-2 [154]. Besides the monoclonal antibodies that modulate the TNF-α responses, etanercept was suggested as another immunomodulator for COVID-19 patients [147].

Lenalidomide and thalidomide, which are not specifically classified as TNF-α blockers, were hypothesized to be repurposed based on a drug-gene interaction analysis [141]. Thalidomide has anti-inflammatory, anti-fibrotic, and immunoregulatory effects, which proved to be safe and effective in the treatment of lung injuries with different etiologies, including H1NI-induced lung injury [155]. It has also entered a clinical trial of COVID-19, as shown in Table 5.

CD24Fc, which is a fusion protein constituted of human CD24 attached to the human IgG Fc region, is another biological immunomodulator. CD24Fc was demonstrated to successfully ameliorate cytokine responses in viral infections and reduce the graft versus host disease [156,157]. Hence, CD24Fc could be effective against the SARS-CoV-2 cytokine storm and the associated pneumonia. CD24Fc has entered a clinical trial by OncImmune® incorporation (Table 5).

6.3.8. Corticosteroids

The rationale for using corticosteroids in COVID-19 patients relies on their inhibitory effects on the inflammatory factors. Corticosteroids inhibit a massive proportion of cytokines, chemokines, inflammatory enzymes, and receptors that are overexpressed in response to the viral infections [158]. Results regarding the beneficial effects of corticosteroids against coronavirus are controversial. A meta-analysis including 5270 patients from 15 studies revealed that the use of corticosteroids resulted in higher mortality rate, the longer length of stay, a higher rate of bacterial infection, hypokalemia, and hypercalcemia [159]. Furthermore, Russell and colleagues in a comment published in The Lancet did not advocate the use of corticosteroids in COVID-19-induced lung injury or shock, except in the clinical trial settings [160]. By contrast, a retrospective analysis of 401 patients with severe SARS revealed that corticosteroids led to reduced mortality rate and shortened hospital stay [161]. Taken together, corticosteroids are indicated for critically ill COVID-19 patients, and its use in mild to moderate patients is highly disregarded. For instance, the use of corticosteroids is recommended in mechanically-ventilated COVID-19 patients with respiratory failure (with ARDS), while is inappropriate for COVID-19 patients without ARDS [162]. In fact, administering corticosteroids in the onset of disease was shown to deter the immune system and increase the viral load, thereby inducing additional complications, such as diabetes and vascular necrosis [163,164]. The timing and dosage of corticosteroids are of special importance in the outcomes of treatment in critically ill patients [165]. For instance, in patients with high inflammatory responses including severe deterioration of oxygenation indicators and rapid imaging progress, a short term (3–5 days) of corticosteroids doses equivalent to 1–2 mg/kg/day methylprednisolone is recommended [166]. Moreover, a recent study revealed that low doses of corticosteroids (e.g. 25–150 mg/day methylprednisolone) did not delay viral clearance and did not increase the mortality rate compared with the control group [167].

Recently dexamethasone was introduced as the first medicine presented with a survival benefit in treating critically ill COVID-19 patients, and WHO welcomes preliminary results regarding its use [168,169]. According to a large, multi-center and randomized clinical trial called RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial, the use of 6 mg/day dexamethasone in COVID-19 patients on mechanical ventilation or oxygen supplementation was associated with reduced mortality rate compared with those who received an standard treatment. In the patients who did not need respiratory support, no improvement was observed [170,171]. This well-known steroid is believed to support the suppression of hyperactive inflammatory responses, so-called cytokine storm [168]. Interestingly, an extra mechanism in defeating SARS-CoV-2 by dexamethasone was suggested. A

computational study revealed that dexamethasone tightly binds to 3C-like protease (the main protease) in SARS-CoV-2 as remdesivir does; however, dexamethasone surprisingly forms a better contact with the enzyme active site than remdesivir [172].

In addition to the importance of dose and timing, other considerations concerning the use of corticosteroids ought to be made according to a recent correspondence consensually made by experts in The Lancet, including: 1) the pros and cons of corticosteroids should be carefully evaluated prior to administration; 2) prudent consideration should be made for the further use of corticosteroids in patients who are on the regular use of corticosteroids for chronic diseases [173].

7. Conclusion

Modulation of the immune system is obviously a major strategy in the control and treatment of COVID-19, which should be adjusted according to different stages of the disease. It can be done through vaccines, interferons, antibodies (either as convalescent plasma therapy or monoclonal and polyclonal antibodies), or potential therapeutic immunomodulators.

At the pre-disease or disease prevention stage, active immunization by vaccines could be an optimal approach. However, vaccine development is a time-consuming and complicated process. Despite enormous efforts in finding vaccines against SARS-CoV-2, there is still a fairly long way to the market availability of a proper vaccine.

At the early stages of the disease, stimulation of the immune system through passive immunotherapy is regarded as a therapeutic objective to support the patient's immune system and compensate for its suppression by SARS-CoV-2. CPT, as a viable emergency immunotherapy, is already being investigated in many countries with positive results. Yet, some limitations of CPT suggest the employment of manufactured monoclonal or polyclonal antibodies. Given the specificity of antibodies, using a cocktail of monoclonal antibodies, which can target SARS-CoV-2 in several locations, is proposed to prevent viral entry into the host cells more thoroughly. The higher speed of antibody development process versus vaccines and small molecules are regarded as the benefits of antibody therapy for the management of COVID-19. However, the probability of adverse events caused by antibody administration such as disease aggravation through antibody-dependent enhancement (ADE) and the intensification of inflammatory responses and worsening of the disease should be taken into serious consideration. Designing novel antibodies with strong viral neutralization capability and less proinflammatory function could be a new research avenue.

In critically ill COVID-19 patients, at the later stages of the disease, dysregulation of the immune system may occur, which may lead to a cytokine storm. In such conditions, immunosuppression by JAK inhibitors, mTOR inhibitors, TNF-α blockers, corticosteroids, or other immunosuppressant and anti-inflammatory drugs could be potentially the life-saving strategy. Currently, the efficacy and adverse effects of different drugs of these categories are under evaluation in clinical trials to completely evaluate their risk and benefits and avoid the possibility of unwanted immune suppression in favor of the virus replication and proliferation in the body. Recently, the survival benefit of low dose dexamethasone was reported in hospitalized patients.

Despite the similarities of SARS-CoV-2 with SARS and MERS, some differences such as higher transmission rate and longer incubation period indicate its varied interaction with the immune system. Given that most of the present data are interpreted from SARS and MERS studies, more specific data about SARS-CoV-2 immunopathogenicity and viral-mediated responses are demanded. Finally, taking into account the complexity of the immune system activities and their complicated interconnections, a systemic approach could be a key element in gaining a more complete picture of this disease and the virus pathogenicity. Such insight is urgently warranted to plan for proper interventional therapies with predictable and favorable outcomes.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106924.

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