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Review

Novel insights into the treatment of SARS-CoV-2 infection: An overview of current clinical trials

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ABSTRACT

The emergence of the global pandemic caused by the novel SARS-CoV-2 virus has motivated scientists to find a definitive treatment or a vaccine against it in the shortest possible time. Current efforts towards this goal remain fruitless without a full understanding of the behavior of the virus and its adaptor proteins. This review provides an overview of the biological properties, functional mechanisms, and molecular components of SARS-CoV-2, along with investigational therapeutic and preventive approaches for this virus. Since the proteolytic cleavage of the S protein is critical for virus penetration into cells, a set of drugs, such as chloroquine, hydroxychloroquine, camostat mesylate have been tested in clinical trials to suppress this event. In addition to angiotensin-converting enzyme 2, the role of CD147 in the viral entrance has also been proposed. Mepolizumab has shown to be effective in blocking the virus's cellular entrance. Antiviral drugs, such as remdesivir, ritonavir, oseltamivir, darunavir, lopinavir, zanamivir, peramivir, and oseltamivir, have also been tested as treatments for COVID-19. Regarding preventive vaccines, the whole virus, vectors, nucleic acids, and structural subunits have been suggested for vaccine development. Mesenchymal stem cells and natural killer cells could also be used against SARS-CoV-2. All the above-mentioned strategies, as well as the role of nanomedicine for the diagnosis and treatment of SARS-CoV-2 infection, have been discussed in this review.

Contents

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1. Introduction

The harm wreaked by infectious agents, particularly viruses, among the world's population has a very long history and has periodically challenged human life every few years. Viral infections (especially respiratory viruses) have accounted for a large proportion of epidemics and pandemics to date. Discovering an effective vaccine and implementing a correct vaccination program has led many of these viruses to be eradicated or at least severely restricted. Following the outbreak of any widespread viral disease, studies from around the world should be initiated to undertake the design of an effective vaccine. One of the most important viral families, which have always been a major concern for researchers in vaccine design, is the Coronaviridae family. Viruses of this family can periodically infect humans, causing mainly severe respiratory syndromes, ranging from Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), to the novel pandemic coronavirus SARS-CoV-2, the causative agent of Coronavirus Disease 2019 (COVID-19).

Coronaviridae family contains RNA viruses that usually infect the respiratory tracts of mammals and birds, and can cause several illnesses, which so far have rarely resulted in death. Although coronaviruses have infected different animal species for a long time, the first coronavirus with the ability to infect humans was only identified in the 1960s [1]. Further studies revealed that two human coronaviruses, HCoV-229E, and HCoV-OC43 were able to cause a common cold syndrome with symptoms akin to colds caused by rhinoviruses [2]. The severe morbidity of coronaviruses in humans became more evident after the identification of SARS-CoV in 2003, HCoV-NL63 in 2004, HKU1 in 2005 [3], MERS-CoV in 2012 [4], and finally SARS-CoV-2 in 2019 [5], which all cause severe respiratory tract infections with the danger of wide-scale mortality.

The COVID-19 and its causative infectious agent, SARS-CoV-2, became a global problem in early 2020, and this horrible disease has threatened the survival of millions of people around the world with a mortality rate of approximately 5–10% [6]. So, there is an urgent need to find ways either to confine the spread of the virus or effectively treat its complications. Among our options, vaccination seems to the best route to our salvation. Due to the genomic and proteomic features of the virus such as the "template switching" (i.e. viral RNA mutations even in the amino acid stage) and despite numerous international efforts to design a vaccine to prevent the infection by this novel human virus, we still face many challenges to supply an effective vaccine, especially on a global scale [7]. The ongoing research into COVID-19 vaccines could light the road ahead for further studies aimed at finding an effective and affordable vaccine for preventing this novel dreadful disease. The present review focuses on these efforts and provides several insights into the accomplishments, failures, and risks of developing SARS-CoV-2 vaccines.

2. Origin and evolution of highly pathogenic coronaviruses

Coronaviruses are zoonotic viruses that naturally infect animals, but can be transmitted from animals to humans and have a powerful ability to infect human cells. Taxonomically, the highly pathogenic coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) are classified into the *Nidovirales* order, *Coronaviridae* family, *Coronavirinae* subfamily, and also into the *Betacoronavirus* genus (International Committee on Taxonomy of Viruses).

Human angiotensin-converting enzyme II (ACE2) is the main receptor for SARS-CoV, by which the SARS-CoV S protein enters the host cells. The viral attachment protein or Spike protein binds to ACE2 via the receptor-binding domain (RBD) located on the surface of S protein [8]. Interestingly, structural analysis of the RBDs from S proteins derived from different strains of SARS-CoV has shown that the RBDs have a different affinity for the ACE2 receptor in several animal models. For example, the strain hTor02 of SARS-CoV (the epidemic strain) contains RBDs which have a high affinity for human ACE2, and enable the virus to infect human cells easily [9].

The structural and genomic analysis of SARS-CoV-2 with the viruses isolated from other different species showed that another probable host of the SARS virus might be the pangolin. However, it is hard to be sure whether bats are the primary host or pangolins (Fig. 1a) [10].

3. Structural and immunological characterization

The complete structure of the coronavirus virion, as the largest known RNA virus, contains a positive-sense, non-segmented, single-stranded RNA combined with the nucleocapsid (N) proteins assembled into a helical shape. A phospholipid bilayer structure similar to a mammalian cell membrane covers the RNA, and a high number of M proteins and S proteins are located in this layer. The membrane (M) and envelop (E) proteins can be found among these S proteins (Fig. 1d) [11]. When this virus infects a human cell, the immune system is triggered into action to eliminate the virions, and destroy infected cells. As the first line of defense against viral infections, the innate immune response starts its fight against the virus by producing inflammatory cytokines and chemokines. The most important innate immune response mediators involved in the initial defense against coronavirus include RIG-I-like receptors (RLRs), C-type lectin-like receptors (CLRs), toll-like receptors (TLRs), NOD-like receptors (NLRs), and also cytoplasmic receptors such as cGAS, IFI16, STING, and DAI [11]. However, although the activation of the innate immune response is designed to clear infected tissue from the virus, it can also be dangerous and harmful for healthy tissues [12]. Natural killer (NK) cells are the crucial immune cells of the innate immune response, with the ability to deal with the viral infections and kill infected cells by producing perforin or inducing IFN-γ. It has been reported that NK cells are decreased in the serum level of patients with SARS-CoV infection [13]. To prove this concept, a mouse model of SARS was used to show that NK cells were not necessary for the clearance of SARS-CoV [14]. On the other hand, plasma analysis of SARS patients showed that mannose-binding lectins (MBLs) and serum amyloid A (both acute-phase proteins) were elevated in a calcium-dependent manner and MBLs could bind to the S proteins of SARS-CoV to exert their protective effects [15]. The production of IFNs is an

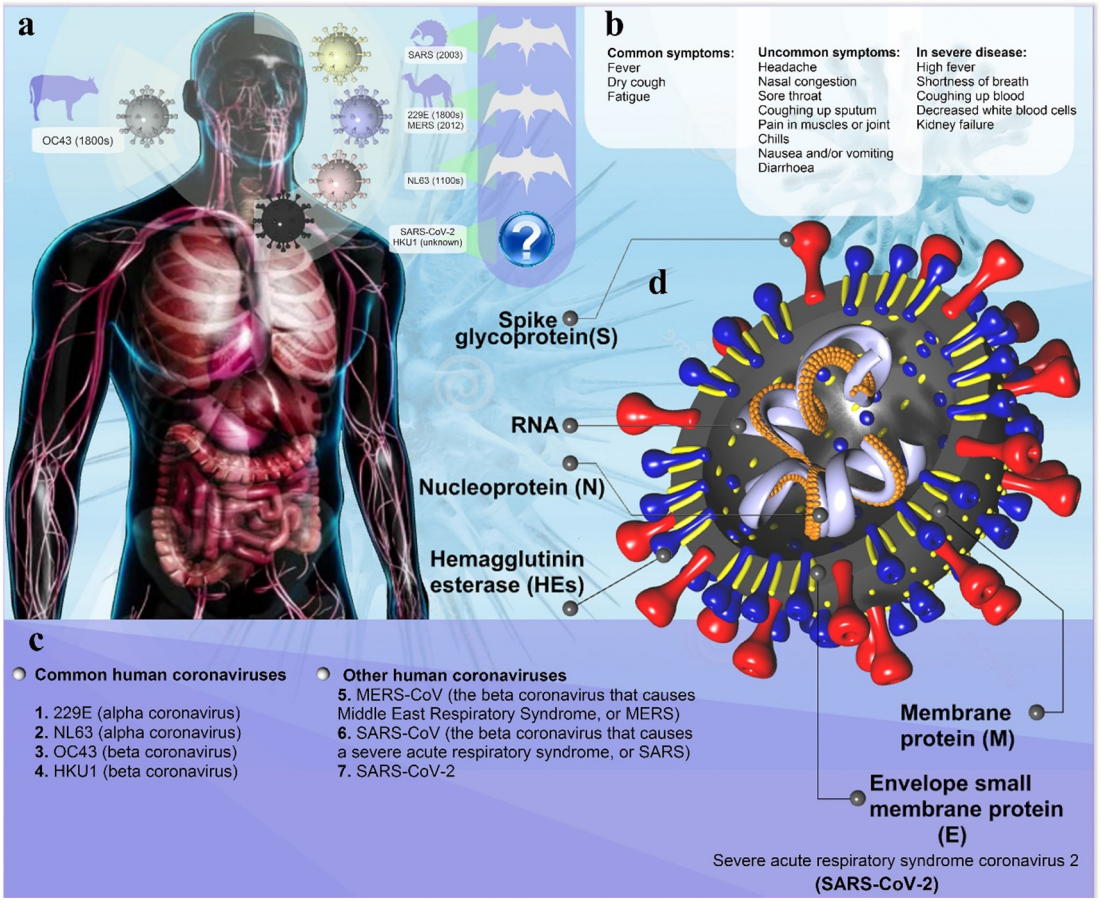

Fig. 1. Coronavirus pathophysiology. (a) Animal (natural and intermediate hosts) origin of human coronaviruses; Pangolins may be intermediate hosts for transmission of the new SARS-CoV-2 from bats to humans. Although cats can be infected with the SARS-CoV-2, and can spread it to each other, dogs have only a low susceptibility to this virus. However, the existence of intermediate animal host(s) of SARS-CoV-2 is still likely. (b) Clinical presentation of patients with SARS-CoV-2, including common, uncommon, and severe symptoms of SARS-CoV-2. (c) Human Coronavirus Types: common human coronaviruses; 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus) and other human coronaviruses; MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus that causes the severe acute respiratory syndrome, or SARS), SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19); d) Diagram of coronavirus virion structure showing genome and structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N).

essential antiviral mechanism functioning as a chemo-attractant mechanism to attract immune cells to eliminate infected cells, as well as to protect non-infected-cells. SARS-CoV inhibits the function of IFN via hindering its related pathways; for example, this virus increases the nuclear transport of IFN regulatory factor 3 (IRF3) to repress the IFN response [16]. Regarding the inflammatory functions of macrophages and dendritic cells (DCs), SARS-CoV non-specifically infects these immune cells, as well as peripheral blood mononuclear cells (PBMCs) giving rise to the production of several chemokines, including IFN-inducible protein 10 (IP-10), RANTES (CCL5), macrophage inflammatory protein 1 α (MIP-1α), and monocyte chemoattractant protein 1 (MCP-1), all of which subsequently increase the level of inflammation in SARS-CoV-infections [17,18].

During a viral infection, and especially a coronavirus infection, not only is there an innate immune response, but the adaptive immune response is also activated in the host. Cytotoxic T lymphocytes mostly function during cellular immunity to eliminate the virally infected cells. The S proteins of SARS-CoV have two HLA-A2-restricted T cell epitopes that can activate T cells responses in SARS-positive patients [19]. Surprisingly, lymphopenia has been observed during SARS-CoV infection, and this reduction was more pronounced in CD4+ T cells compared to CD8+ T cells [20]. It has been demonstrated that an IgG against the N protein of SARS-CoV is the first antibody produced after primary infection [21]. However, antibodies against the S protein have been reported to have neutralization effects on SARS-CoV virions [22]. These antibodies could also trigger the phagocytosis of infected-cells by MΦs, leading to an elevated level of proinflammatory cytokines and chemokines, and subsequent tissue injury due to excessive inflammation [23].

The exact immunopathology mechanisms of SARS-CoV-2 and its related disease, COVID-19, are still under investigation. Indeed, the cytokine storm and incidence of inflammation in lungs have been found to be the leading causes of acute respiratory distress syndrome (ARDS) in COVID-19 patients just like it occurs with SARS patients (Fig. 2) [24].

4. Cell entry mechanism and therapeutic implications

An understanding of SARS-CoV-2 cell entry mechanisms will facilitate the design of effective therapeutics that could target this critical step in the viral life cycle. The host cell membrane is essential to prevent infection, acting as a barrier between the viral particle and the intracellular site of viral replication [25]. Although not a guarantee of successful infection, the binding and passage of the virus through the cell membrane barrier is a critical step in the life cycle of a virus [26], especially for coronaviruses. Coronavirus entry into a host cell is a dynamic, multi-step cascade process. These viruses access target cells by binding to cell surface receptors, followed by membrane fusion mediated by a multifunctional fusion protein [27,28]. Although there is evidence implicating cellular endocytic pathways for entry of viruses into host cells, the exact mechanisms of entry for many viruses, including coronaviruses, have yet to be fully characterized [29]. Identification of the host cell receptors, the structural binding mechanism, and the

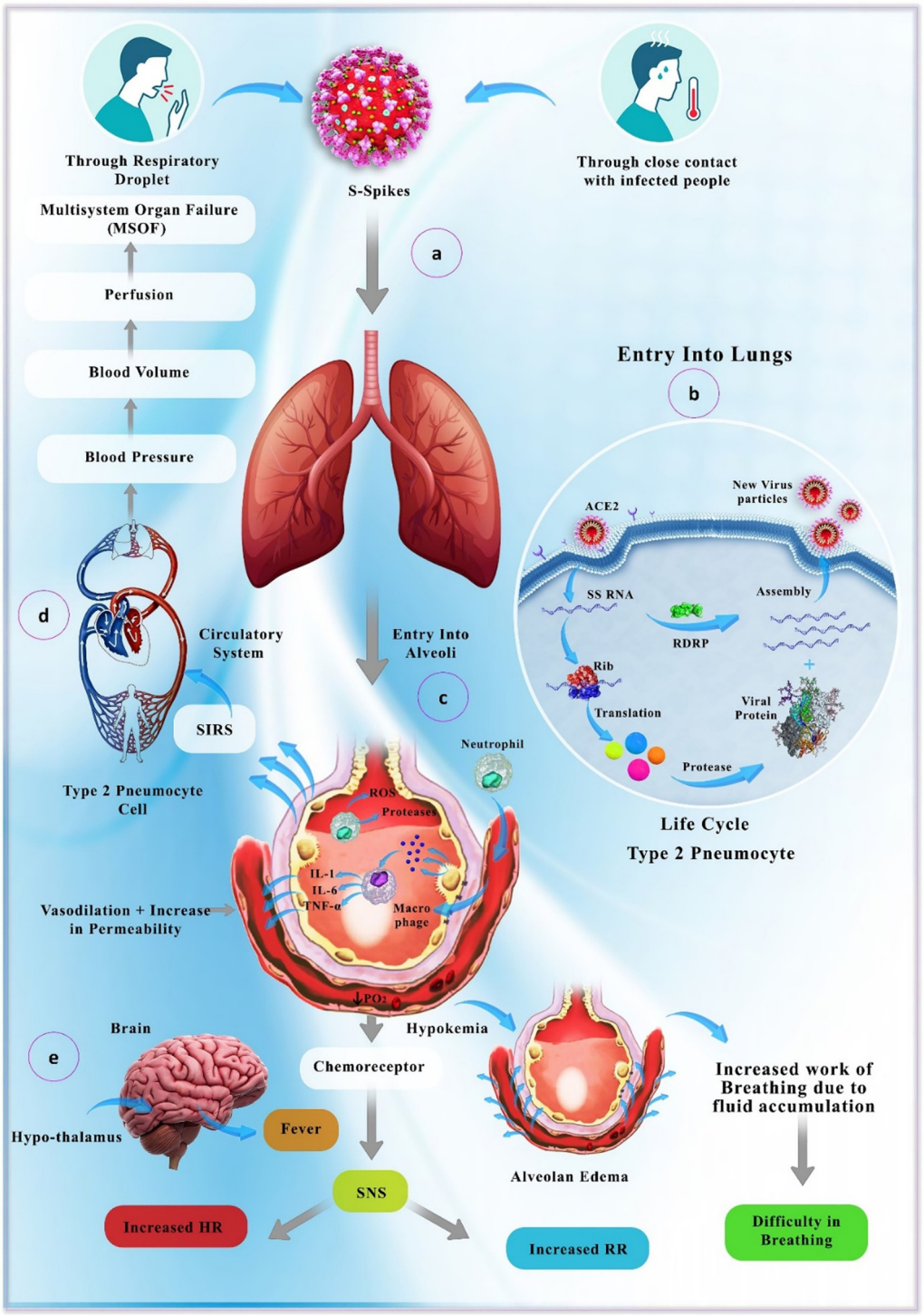

Fig. 2. Transmission and pathology of the SARS-Cov-2 virus. After transmission via droplets from an infected person (a), the virus particles infect and replicate in type 2 pneumocytes (b), which finally results in inflammation of alveoli (recruitment of inflammatory cells and secretion of inflammatory mediators) (c) and disruption of respiratory and blood circulation systems. Finally, multi-organ dysfunction occurs due to the severe hypoxia and lack of perfusion (d). Reduction in PO2 and fluid accumulation in alveoli further aggravates the clinical condition and leads to pulmonary, as well as cerebral manifestations (e). SIRS: systemic inflammatory response syndrome; RDRP: RNA-dependent RNA polymerase.

virus trafficking pathway will support the development of therapeutic agents against SARS-CoV-2.

4.1. Host membrane proteins render cells susceptible to SARS-CoV-2

In the classical pathway, viruses enter host cells via endocytosis, following binding to cell surface receptors. Viruses can physically penetrate cells by endocytic cellular uptake in a process usually referred to as receptor-mediated endocytosis [30]. Angiotensin-converting enzyme 2 (ACE2) is a critical type 1 integral membrane protein, which is expressed in most human and some animal tissues. ACE2 is highly expressed in the endothelium, the lungs, and the heart [31]. When this cell surface protein was discovered three decades ago, neither of the research groups involved could have appreciated the large number of distinct functions this receptor plays in biology, from viral infection to cardiovascular regulation [32]. ACE2 is the first known host receptor for

SARS-CoV-2 [33], and it was found that SARS-CoV-2 does not use other host cell membrane proteins, such as dipeptidyl peptidase 4 (DP IV, CD26) or aminopeptidase N (APN, CD13) [34]. Cao et al. systematically searched for variants of ACE2, which could affect the pathogenesis of SARS-CoV-2 among different populations. Their results showed that was little evidence of genetic variations supporting the existence of susceptibility or resistance in diverse populations. East Asian populations had much higher frequencies in the eQTL allele variants, which may govern different responses to SARS-CoV-2 in different populations [35]. In addition to ACE2, Wang et al. reported that SARS-CoV-2 could enter target cells through a novel interaction of the viral proteins with CD147 [36]. CD147, also known as basigin or extracellular matrix metalloproteinase inducer (EMMPRIN), is expressed in a variety of human cells. CD147 regulates extracellular matrix remodeling during many critical biological processes, including cancer, inflammatory disease, and wound healing [37]. It could be the case that some SARS-CoV-2 receptor variants and expression levels in different patients may be associated with more severe forms of the infection.

Increased viremia (level of viruses in the bloodstream and other bodily fluids) leads to higher severity of infection [38]. During viremia, the human circulatory system facilitates the transport of viruses throughout the entire body. Coronavirus viremia mainly appears one week after the onset of symptoms. Viremia then decreases gradually over a week, becoming undetectable in the bodily fluid samples of convalescent patients [39]. ACE2 is widely expressed in other tissues and cell types, such as cardiomyocytes, cardiofibroblasts, and coronary endothelial cells [40]. CD147, in a similar manner to ACE2, is expressed in many different epithelial, neuronal, lymphoid, and myeloid cell types [41]. Over-expression of these receptors in different tissues and cell types could explain subsequent syndromes such as myocarditis or encephalopathy. Therefore, ACE2/CD147-based therapeutics could inhibit the binding of SARS-CoV-2 to its receptors and prevent the coronavirus from invading its target cells, possibly providing a strategy for the development of anti-SARS-CoV-2 drugs.

4.2. The spike protein of SARS-CoV-2 promotes cell entry

Coronavirus cell entry relies on an interaction between the surface receptor of target cells and the spike (S) proteins of coronaviruses, which mediates viral entry [42]. The Coronavirus S protein is a trimeric type I transmembrane protein with 1160 to 1400 amino acid residues. SARS-CoV and S SARS-CoV-2 proteins are highly glycosylated at 21 to 35 sites, which all have 76.5% identity in amino acid sequences and a high degree of homology (Fig. 3a) [43,44]. These glycoproteins assemble on the coronavirus surface, forming a crown-like array that gives this virus its name (crown = corona). The crystallization of the S protein of SARS-CoV-2 and examination by cryo-electron microscopy showed the role of these sites in the interplay between SARS-CoV-2 S and its target cell receptors [45]. Interestingly, these coronaviruses contain a critical loop with flexible residues. Replacing this loop with other amino acid residues, such as those from SARS-CoV using molecular modeling, showed that the receptor-binding domain has a higher affinity for host cell receptors compared with other coronavirus S proteins (Fig. 3b right) [46].

Recent publications have reported that coronavirus entry is a multistep process requiring several domains in the S protein [21]. An interplay between a single region of the SARS-CoV-2 S protein called the receptor-binding domain (RBD), and the protease domain (PD) of ACE2 [47] prompts endocytosis of the virus. This interaction then mediates the fusion between the viral particle and the target cell membrane, allowing endocytosis into the cytosol [26] (Fig. 2c). Structures of PD (alone and in complex with the RBD) have revealed the molecular details of the interaction between the RBD and PD [48,49]. Yan et al. demonstrated the three-dimensional structure of ACE2 in a dimeric assembly. Molecular docking studies suggested the simultaneous binding of the ACE2 dimer to two coronavirus S protein trimers [33]. The S protein RGD binds to the RBD at the border of the subdomain (amino acids 437 to 508) [44,50,51]. Residue 479 in SARS-CoV RBD corresponds to residue 394 in the SARS-CoV-2 RBD, and is recognized by the critical residue 31 in the ACE2 enzyme [52,53]. This interaction is now known to trigger a conformational change within the viral S protein, which then mediates fusion of the host cell membrane and the SARS-CoV-2 viral membrane allowing the genetic material to be introduced into the target cell.

4.3. SARS-CoV-2 uses multiple pathways for S protein activation

Viruses deliver their genetic material into target cells using a variety of strategies and molecules [54]. The viral S glycoprotein contains multiple cleavage sites. S glycoproteins contain two domains: a C-terminal S2 domain and an N-terminal domain named S1 (Fig. 2a and c). When the S1 subunit binds to ACE2, the S2 cleavage site is then cleaved by host proteases [33]. The coronavirus fusion peptide is located downstream from the S2 N terminus. This critical peptide forms a loop and a short helix, and contains nearly all the hydrophobic residues buried inside the prefusion structure [42,55]. Following host cell binding, the coronavirus S proteins undergo conformational changes exposing hydrophobic domains and the fusion peptide, which becomes embedded into the host cell cytoplasmic membrane. The pre-fusion to post-fusion transition in the S protein is irreversible and is regulated during the cell entry [42,56]. In the next stage, S protein subdomains become refolded into a heptad repeat 1 (HR1), which initiates the endocytosis of coronaviruses (Fig. 4) [57].

Different co-receptors have been identified to be involved in virus entry into the host cells and control the efficiency of cell entry [58]. When S proteins bind to host cell receptors, they encounter cellular co-receptors and activators. These co-receptors and activators may be membrane receptors, transmembrane receptors, proteases, or cations, which facilitate viral fusion protein refolding into an active form that catalyzes host cell membrane coalescence [59]. Many of these molecules are cellular proteases that cleave and activate the S proteins in ways that expose the essential domain for virus fusion [60]. These host cell proteases include trypsin, cathepsins, elastase, thermolysin, furin, the proprotein convertase family, and transmembrane protease/serine (TMPRSS) [61]. TMPRSS11d and TMPRSS2 can both induce coronavirus fusion. When host cells express TMPRSS2, infection of pulmonary cells with coronavirus S-pseudotyped particles was less sensitive to inhibitors of cathepsins B and L. In pulmonary cells, coronavirus S protein employs TMPRSS2 for S protein priming, and the endosomal cathepsins B and L are not essential for viral entry [62–64]. Therefore, further work is needed to assess which co-receptors and activators can enhance the entry of SARS-CoV-2 at the level of S protein.

4.4. SARS-CoV-2 cell entry inhibitors

SARS-CoV-2 entry into cells is a critical step of its life cycle that can be used as a target for treatment. Antiviral molecules that inhibit the host cell entry of coronaviruses have been reported. For example, Adedeji et al. identified compounds that could inhibit coronavirus cell entry through different mechanisms. The first identified inhibitor of SARS-CoV-2 cellular entry was SSAA09E2 (N-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]-1,2-oxazole-5-carboxamide) that acted through prevention of the ACE2–RBD interaction. SSAA09E1 [(Z)-1-thiophen-2-ylethylideneamino]thiourea, was the second identified compound, which inhibited cathepsin L, and SSAA09E3, [N-(9,10-dioxo-9,10-dihydroanthracen-2-yl)benzamide], suppressed the fusion of the viral particles with the target cells [65]. For human coronaviruses, some other peptides have been reported to inhibit host cell entry through different mechanisms. For instance, Struck et al. demonstrated that a hexapeptide that bound to the ACE2 receptor, could block viral infection of host cells [66].

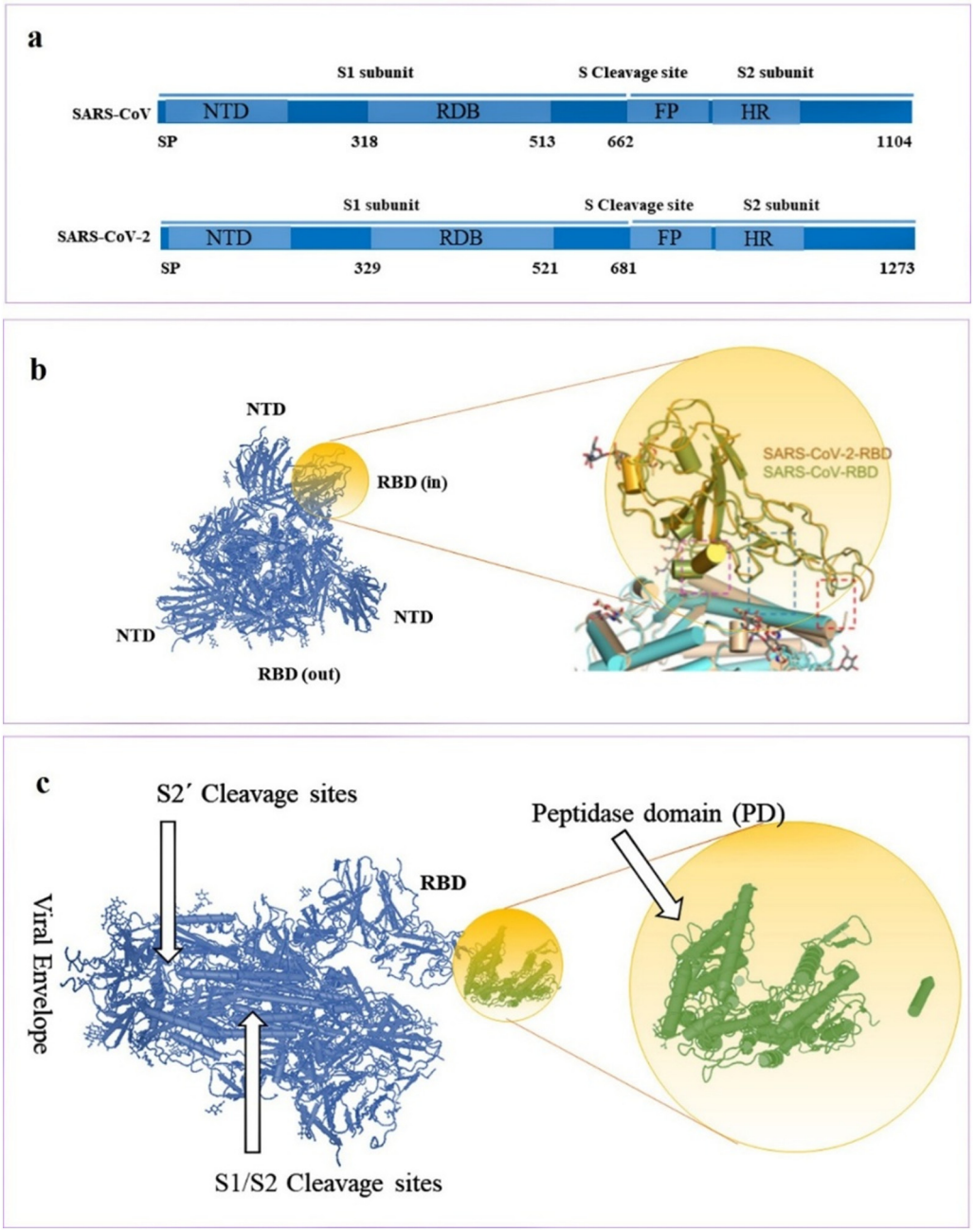

Fig. 3. Molecular detail of coronavirus S proteins and host cell ACE2 protein. a) Phylogenetic analysis of SARS-CoV and SARS-CoV-2 S proteins. b) Structural alignment and structure of RBD for the SARS-CoV and SARS-CoV-2 [33]. c) SARS-CoV-2 S protein cleavage sites and its interaction with the PD of ACE2 (Protein Data Bank ID: 6VYB and 1R42).

As mentioned, SARS-CoV-2 uses specific receptors, ACE2, and CD147, which are expressed on human airway epithelial cells and lung parenchyma. Compounds that act as angiotensin receptor blockers have been in clinical use since 1995, and are known to be effective antihypertensive agents with excellent tolerability profiles [67]. Many anti-ACE agents that can inhibit the renin-angiotensin system, such as losartan, rifampin, fluconazole, candesartan cilexetil, eprosartan, irbesartan, telmisartan, valsartan, azilsartan medoxomil, and olmesartan medoxomil, have been tested as treatments for hypertension. Other agents that may block the progression of the SARS-CoV-2 infection are angiotensin receptor 1 blockers, such as losartan [68]. Furthermore, anti-CD147 antibodies, such as mepolizumab, could effectively prevent the coronaviruses from invading target cells by blocking the CD147 receptor. These strategies may be reliable and safe without being affected by virus variation and mutation [36]. Interestingly, Hoffmann et al. reported that target cell entry of SARS-CoV-2 could be blocked by camostat mesylate, an inhibitor of TMPRSS2, which is employed for S protein priming [62]. A summary of the clinical trials against SARS-CoV-2, using hydroxychloroquine, chloroquine, losartan, mepolizumab, camostat mesylate, and other compounds is provided in Table 1.

5. Small molecule antiviral agents

The development of antiviral drugs against SARS-CoV-2 is difficult. Several clinical trials of antiviral agents have been started as of May 2020, now amounting to a total of 306 active trials. Up to now, protease inhibitors, including ritonavir, oseltamivir, darunavir, and lopinavir, have been the most frequently tested class of drugs for the treatment of COVID-19. Lopinavir and ritonavir are HIV protease inhibitors,

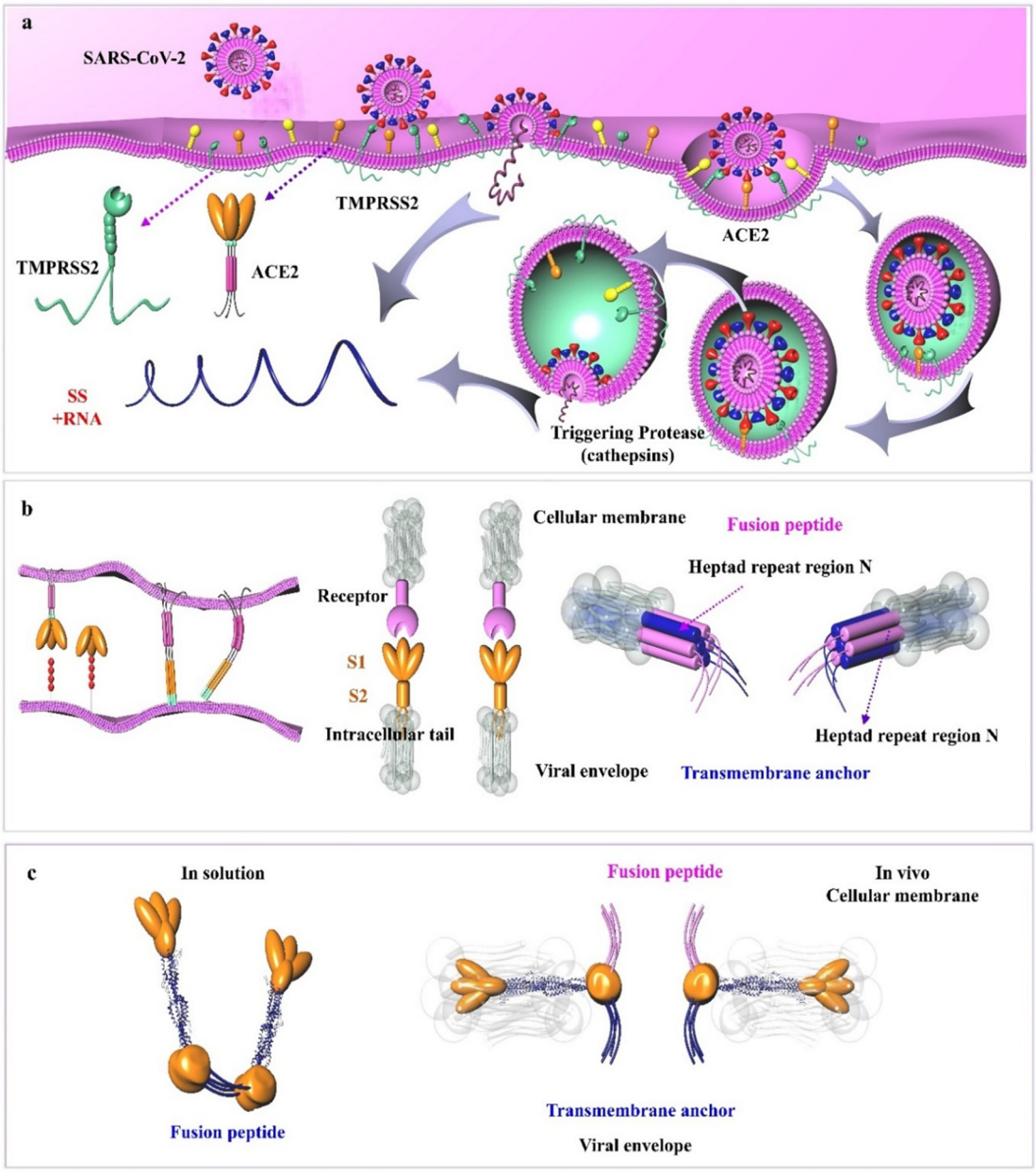

Fig. 4. SARS-CoV-2 cell entry mechanisms and subsequent intracellular trafficking. a) Role of host cell proteases in the cellular entry of SARS-CoV-2. Host cell entry of SARS-CoV can proceed via two distinct routes; in the absence of SARS-S-activating protease, the virus is internalized via the binding of SARS-S to ACE2 on the surface of host cells. Within the endosomes, the SARS-S is then cleaved and activated by cathepsin L, a pH-dependent cysteine protease. The SARS-S may also be activated by TMPRSS2 on the membrane surface of host cells when this protease is expressed along with ACE2 allowing the fusion of two membranes (i.e., host and the virus) and viral entrance. b) The role of class I transmembrane proteins expressed on the surface of SARS-CoV-2 in promoting membrane fusion. Conformational changes of these proteins before and after fusion have been shown. c) The conformation of the viral S2 protein has also been indicated in vitro (left) and in vivo (right). Abbreviations: FP, fusion peptide; HR-N, heptad repeat region N; HR-C, heptad repeat region C; IC, intracellular tail; SARS-CoV-2, severe acute respiratory syndrome coronavirus; TM, transmembrane anchor.

which have shown some promise in the treatment of SARS-CoV-2 infection [69], and have been tested in trials in COVID-19 patients [70,71]. For example, the third patient diagnosed with SARS-CoV-2 in Korea was treated with lopinavir and ritonavir starting from hospital day 8. After treatment, very low coronavirus titers were observed compared with a control group of untreated patients [72]. Cao et al. conducted a clinical trial using a combination of lopinavir with ritonavir as a potential treatment for hospitalized COVID-19 patients. However, these drugs showed no significant effect beyond standard care [70]. In addition, anti-influenza drugs that are routinely used in clinical practice, including neuraminidase inhibitors (zanamivir, peramivir, oseltamivir, etc.), acyclovir, ribavirin, ganciclovir, and methylprednisolone [73,74], have been studied as anti-SARS-CoV-2 drugs in clinical trials. Darunavir is a protease inhibitor primarily targeting the HIV-1 virus, which is being tested in clinical trials for SARS-CoV-2 treatment. Future clinical trials of protease inhibitors in patients with severe viral respiratory infections may help to exclude or confirm the possibility that they could be beneficial agents.

RNA-dependent RNA polymerase (RdRp) inhibitors are the second most frequently used class of drugs in the treatment of SARS-CoV-2 patients. Compared to the conserved sequence of RdRp in coronaviruses, SARS-CoV-2 and SARS-CoV have similar sequences and structures of RdRp [75]. Nucleoside analogs are generally adenine or guanine derivatives, which block viral RNA synthesis through targeting the RdRp in a broad spectrum of viruses, including human coronaviruses [76,77]. Both approved nucleoside analog drugs in clinical use (sofosbuvir,

Table 1
Selected therapeutic agents as inhibitors of SARS-CoV-2 cell entry currently in clinical trials.

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
2	GlaxoSmithKline	● GSK2586881	Completed	44 18–80	NCT01597635
2	University of Minnesota	● Losartan	Recruiting	516 ≤18	NCT04311177
4	Ruijin Hospital	● Arbidol ● Basic treatment	Not yet recruiting	380 18–75	NCT04260594
4	Beijing YouAn Hospital	● Carrimycin ● Lopinavir with ritonavir tablets or arbidol or chloroquine phosphate ● Basic treatment	Not yet recruiting	520 18–75	NCT04286503
2, 3	Bassett Healthcare	● Lopinavir with ritonavir ● Hydroxychloroquine sulfate ● Losartan	Recruiting	4000 ≤18	NCT04328012
4	Instituto de Investigación Marqués de Valdecilla	● Hydroxychloroquine ● Control group	Not yet recruiting	800 18–75	NCT04330495
4	Wroclaw Medical University	● Chloroquine phosphate ● Telemedicine	Not yet recruiting	400 ≤18	NCT04331600
3	Massachusetts General Hospital	● Hydroxychloroquine	Recruiting	510 ≤18	NCT04332991
1	University of Washington	● Hydroxychloroquine sulfate ● Vitamin C	Not yet recruiting	2000 18–80	NCT04328961
2	Asan Medical Center	● Lopinavir with ritonavir ● Hydroxychloroquine sulfate	Recruiting	100 18–99	NCT04307693
2, 3	Oslo University Hospital	● Hydroxychloroquine ● Remdesivir ● Standard of care	Recruiting	700 ≤18	NCT04321616
3	Rajavithi Hospital	● Protease inhibitors, oseltamivir, favipiravir, and chloroquine	Not yet recruiting	80 18–100	NCT04303299
3	Shanghai Public Health Clinical Center	● Hydroxychloroquine	Completed	30 ≤18	NCT04261517
3	Population Health Research Institute	● Azithromycin ● Chloroquine	Not yet recruiting	1500 18	NCT04324463
3	Hospital do Coracao	● Hydroxychloroquine oral product ● Hydroxychloroquine with azithromycin	Recruiting	630 18	NCT04322123
2	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	● Tocilizumab ● Hydroxychloroquine ● Azithromycin	Recruiting	276 ≤18	NCT04332094
3	University Hospital, Angers	● Hydroxychloroquine	Recruiting	1300 ≤18	NCT04325893
3	University of Minnesota	● Hydroxychloroquine	Recruiting	3000 ≤18	NCT04308668
Not applicable	University of Oxford	● Chloroquine	Not yet recruiting	10,000 ≤16	NCT04303507
1	Sanofi	● Hydroxychloroquine SAR321068	Recruiting	210 ≤18	NCT04333654
2	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado	● Chloroquine diphosphate	Recruiting	440 18–100	NCT04323527
3	Institut National de la Santé Et de la Recherche Médicale, France	● Remdesivir ● Lopinavir with ritonavir ● Interferon beta-1A ● Hydroxychloroquine ● Standard of care	Recruiting	3100 ≤18	NCT04315948
3	Hospital Israelita Albert Einstein	● Hydroxychloroquine with azithromycin ● Hydroxychloroquine	Recruiting	440 ≤18	NCT04321278
4	Chronic Obstructive Pulmonary Disease Trial Network, Denmark	● Azithromycin ● Hydroxychloroquine	Recruiting	226 All	NCT04322396
2, 3	Columbia University	● Hydroxychloroquine	Not yet recruiting	1600 ≤18	NCT04318444
3	National Institute of Respiratory Diseases, Mexico	● Hydroxychloroquine	Recruiting	400 18	NCT04318015
2	University of Pennsylvania	● Hydroxychloroquine Sulfate	Recruiting	400 ≤18	NCT04329923
Early 1	Rambam Health Care Campus	● Hydroxychloroquine	Not yet recruiting	1116 ≤18	NCT04323631
3	Barcelona Institute for Global Health	● Hydroxychloroquine	Recruiting	440 ≤18	NCT04331834
Early phase 1	Azidus Brasil	● Hydroxychloroquine sulfate ● Azithromycin tablets	Not yet recruiting	400 ≤18	NCT04329572
3	Gangnam Severance Hospital	● Hydroxychloroquine as post-exposure prophylaxis	Not yet recruiting	2486 18–99	NCT04330144
3	National Institute of Respiratory Diseases, Mexico	● Hydroxychloroquine	Recruiting	500 18–80	NCT04315896

(continued on next page)

Table 1 (*continued*)

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
3	Centre Hospitalier Universitaire de Saint Etienne	● Hydroxychloroquine ● Lopinavir and ritonavir	Recruiting	1200 ≤18	NCT04328285
2	Korea University Guro Hospital	● Ciclesonide metered dose inhaler [Alvesco] ● Hydroxychloroquine	Not yet recruiting	141 18–80	NCT04330586
2	Intermountain Health Care, Inc.	● Hydroxychloroquine ● Azithromycin	Recruiting	300 ≤18	NCT04329832
2	Oxford University Clinical Research Unit	● Chloroquine phosphate	Not yet recruiting	250 ≤18	NCT04328493
3	University of Calgary	● Hydroxychloroquine	Recruiting	1660 ≤18	NCT04329611
3	Ayub Medical College, Abbottabad	● Hydroxychloroquine ● Azithromycin ● Dietary supplement: glucose tablets	Not yet recruiting	75 18–50	NCT04328272
Not applicable	Renmin Hospital of Wuhan University	● DAS181	Recruiting	4 18–70	NCT04324489
Not applicable	Neuromed IRCCS	● ACE inhibitors	Not yet recruiting	5000 All	NCT04318418
Not applicable	Istinye University	● Hydroxychloroquine	Recruiting	80 20–90	NCT04326725
2	Ansun Biopharma, Inc.	● DAS181	Not yet recruiting	280 18	NCT04298060
1, 2	Tang-Du Hospital	● Meplazumab (a humanized anti-CD147 antibody) for injection	Recruiting	20 18–75	NCT04275245
3	Ansun Biopharma, Inc.	● DAS181 ● DAS181 SARS-CoV-2 ● DAS181 OL	Recruiting	250 All	NCT03808922
4	Tongji Hospital	● Abidol hydrochloride ● Abidol hydrochloride combined with interferon atomization	Recruiting	100 18–80	NCT04254874
4	NCT04255017	● Abidol hydrochloride ● Oseltamivir	Recruiting	400 ≤18	NCT04255017

favipiravir, ribavirin, and tenofovir) and experimental drugs (galidesivir and remdesivir) may have potential therapeutic effects against SARS-CoV-2 RdRp (Fig. 5). Remdesivir is an adenosine analog pro-drug with a broad-spectrum antiviral activity that has been shown to inhibit the replication of a wide array of RNA viruses [78,79]. For instance, remdesivir was in clinical trials for the treatment of male Ebola virus disease survivors [80,81]. Remdesivir is presently in clinical trials for the COVID-19 outbreak (Table 2), and in one completed clinical trial showed promising antiviral activity against SARS-CoV-2 infection. Although the FDA has approved only a few antiviral combination treatments for a relatively small number of viral diseases, several combinations of antiviral agents with activity against SARS-CoV-2 are currently being assessed (Table 2). Among the clinical trials in progress, some are testing antiviral agents, such as lopinavir plus ritonavir, as the most common drug combination. Overall, among the new antiviral trials that were commenced in 2020, remdesivir has attracted the most attention for the treatment of SARS-CoV-2.

Azithromycin is a 15-membered macrolide antibiotic, that is distinguished from other macrolides by its extensive and rapid penetration into biological compartments, accompanied by an acceptable serum half-life and a prolonged concentration in tissue [82]. Azithromycin has been effective in vitro against Ebola and Zika viruses [83–85], and some other viral infections of the lower and upper respiratory tracts [86]. Gautret et al. evaluated the effect of azithromycin plus hydroxychloroquine on the respiratory SARS-CoV-2 viral load. The results suggested a positive effect of the combination of azithromycin and hydroxychloroquine [87]. Azithromycin is currently under study for treating hospitalized patients with moderate to severe SARS-CoV-2 infection.

Nevertheless, even after several months from the first appearance of SARS-CoV-2, we still have no definitive drugs to combat the infection. In fact, we are still testing drugs already known to target similar RNA viruses. These drugs have been proposed to interfere with the progression of the SARS-CoV- 2 infections by a multitude of mechanisms. One class of these drugs interferes with the penetration of the virus into cells by inhibiting either membrane attachment (ACE2) or membrane fusion (TMPRSS2). Some other drugs also prevent the formation of endosomes. Nevertheless, after penetration of the viral particles, it is necessary to use agents that inhibit basic biological functions such as protein synthesis (CLpro and PLpro) or DNA replication (RdRp). Furthermore, it may be possible to use modulators of the immune system to increase the antiviral response (e.g., IL-6R). Care should be taken using such drugs as they may worsen clinical symptoms in severely ill SARS-CoV-2 patients, in whom immunosuppressive drugs may actually be more effective (Fig. 6). None of these potential drugs (either alone or in combinations) can be considered definitive treatments without passing extensive and well-designed clinical trials, which are fortunately underway.

In recent studies, it has been stated that dexamethasone, a corticosteroid that has been effective in treating autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis) as well as inflammatory and hepatic disorders and cancer, may be effective in reducing mortality in patients with COVID-19 infection [88,89].

In fact, this corticosteroid was the first medication that brought hope for saving the lives of severely affected patients with the infection. The efficiency of dexamethasone in improving the clinical condition of COVID-19 patients is currently under investigation along with four other drugs (hydroxychloroquine, azithromycin, lopinavir–ritonavir combination, and tocilizumab) and plasma therapy (the RECOVERY trial) [90]. Giving the ability of nanomaterials to be accumulated in macrophages, Lammers et al. suggested that using nano-forms of dexamethasone may augment its impact on the clinical progression of COVID-19 infection [90,91] a notion which certainly needs more evidence.

6. SARS-CoV-2 vaccine platforms

Several preclinical and clinical trials are now underway testing candidate vaccines against SARS-CoV-2. Vaccination against infectious diseases can be a powerful tool for preventing potential outbreaks of

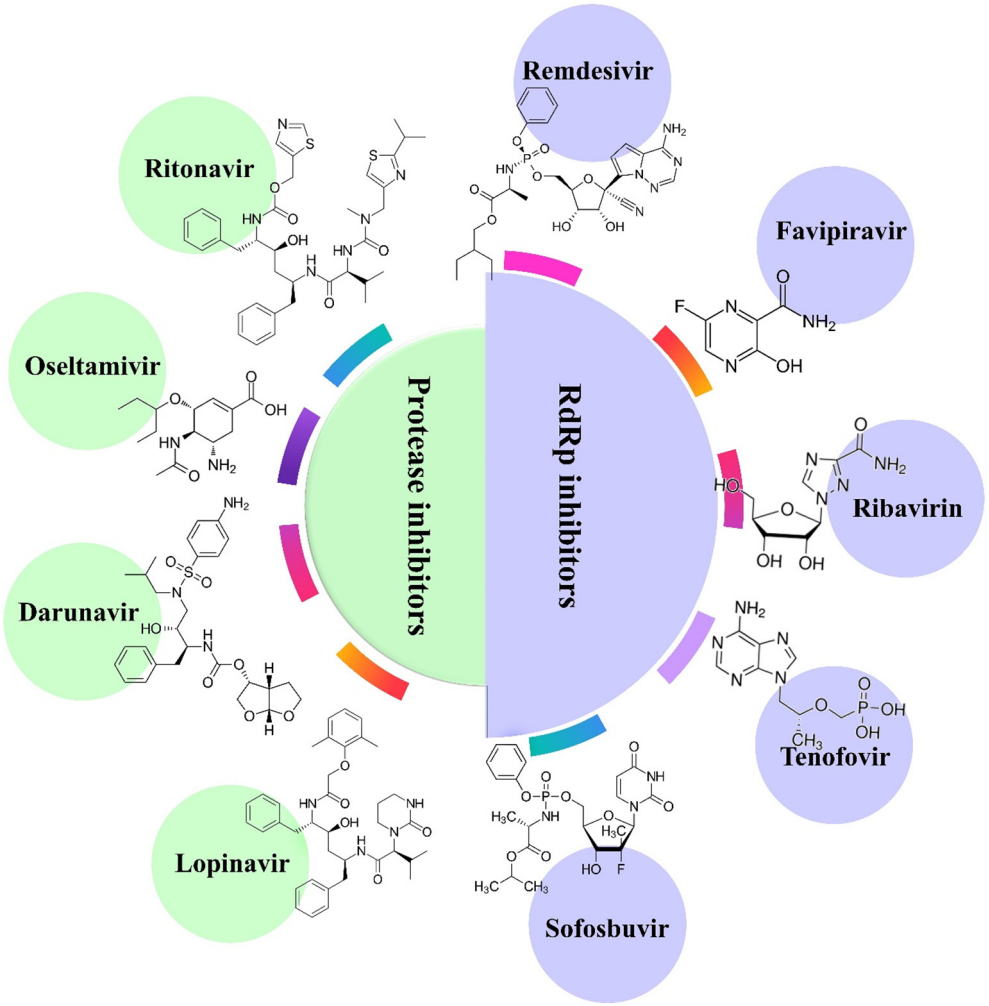

Fig. 5. Potential protease inhibitors and RdRp inhibitors in clinical trials for SARS-CoV-2.

epidemic diseases before they become public health problems [92]. Vaccine strategies are considered as a critical component of SARS-CoV-2 prevention, especially since therapeutic agents are unavailable or ineffective, and that rapid clinical deterioration may limit the effectiveness of any treatment options. The lack of therapeutic vaccines for clinical use against such viruses, makes the coronavirus pandemic a serious global threat [93]. In addition, timely development of SARS-CoV-2 vaccines is needed as soon as possible, not only for controlling the SARS-CoV-2 infection but also for stabilizing the global outlook and bringing the world economy back on track [94]. A number of approaches have been proposed to develop vaccines against coronaviruses [95–98]. SARS-CoV-2 vaccines based on the whole inactivated virus, non-replicating viral vectors, replicating viral vectors, nucleic acids, and subunits, have been tested in preclinical and clinical trials (Tables 3–6). The World Health Organization (WHO) has provided an overview of SARS-CoV-2 candidate vaccines in preclinical trials [99]. However, the enthusiasm for a rapid deployment of SARS-CoV-2 vaccines is tempered by the reality of the experience of developing previous coronavirus vaccines. Although vaccine development against SARS-CoV-2 is under development, manufacturing at scale will take a long time, probably at least 12 to 18 months away from scaled-up vaccine production [100]. Hopefully, SARS-CoV-2 vaccine development can be even faster and more efficient compared to previous experience, and possibly using newer technologies. SARS-CoV-2 vaccine development is still in the early stages. To date, very few SARS-CoV-2 vaccine candidates have been tested in clinical trials (Table 3).

A variety of technological platforms have been exploited in different studies; some of them are briefly described here [101,102] (Fig. 7):

Live attenuated vaccines: Modifying the SARS-CoV-2 virus in a way that reduces its pathogenicity and virulence can assist us in producing a live but weakened virus. Codon deoptimization or introducing a mutated E protein is among methods for making incapable viruses [103]. Although this method can draw a fast and potent immune response, it may not be applicable in immunosuppressed individuals.

Viral-vector based vaccines: Other viruses (e.g., adenovirus) can be used as vectors to carry SARS-CoV-2 genes into cells. This method delivers good immunogenicity even in the absence of an adjuvant. A robust cytotoxic T cell (CTL) response is ensured using such vaccines to remove virus-infected cells.

Recombinant protein-based vaccines: In this approach, a recombinant protein is constructed by adjoining SARS-CoV-2 proteins (such as S protein) with adjuvants. Incorporating adjuvants promote the immune response against the viral antigen.

DNA vaccines: Potentially, we can use plasmid DNA to incorporate target viral genes, which are then expressed to SARS-CoV-2 proteins. By using this method, antigens can be efficiently delivered to host cells. Nevertheless, no approved DNA vaccines are currently available to be used in humans.

mRNA vaccines: Transcripts of SARS-CoV-2 genes (i.e., mRNAs) enclosed in structures such as liposomes can carry viral antigens

Table 2
Selected small molecule therapeutic agents as inhibitors of SARS-CoV-2 in clinical trials.

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
2	Sunnybrook Health Sciences Centre	● Lopinavir with ritonavir	Recruiting	400 ≤6 months	NCT04330690
–	Gilead Sciences	● Remdesivir	Available	– ≤18	NCT04323761
Not applicable	Peking University First Hospital	● Favipiravir with tocilizumab ● Favipiravir ● Tocilizumab	Recruiting	150 18–65	NCT04310228
3	St. Michael's Hospital, Toronto	● Lopinavir with ritonavir	Not yet recruiting	1220 ≤18 months	NCT04321174
–	U.S. Army Medical Research and Development Command	● Remdesivir	Available	–	NCT04302766
3	China-Japan Friendship Hospital	● Remdesivir	Terminated	453 ≤18	NCT04257656
3	China-Japan Friendship Hospital	● Remdesivir	Suspended	380 ≤18	NCT04252664
3	Tongji Hospital	● ASC09F with oseltamivir ● Ritonavir with oseltamivir ● Oseltamivir	Recruiting	60 18–55	NCT04261270
3	Gilead Sciences	● Remdesivir ● Standard of care	Recruiting	600 ≤18	NCT04292730
3	Shanghai Public Health Clinical Center	● Darunavir and cobicistat	Recruiting	30 ≤18	NCT04252274
3	Gilead Sciences	● Remdesivir ● Standard of care	Recruiting	400 ≤18	NCT04292899
3	Germans Trias i Pujol Hospital	● Antiviral treatment and prophylaxis ● Standard public health measures	Recruiting	3040 ≤18	NCT04304053
2	National Institute of Allergy and Infectious Diseases (NIAID)	● Remdesivir	Recruiting	440 ≤18	NCT04280705
2	The University of Hong Kong	● Lopinavir with ritonavir ● Ribavirin ● Interferon Beta-1B	Completed	70 ≤18	NCT04276688
4	The Ninth Hospital of Nanchang	● Ganovo with ritonavir with/and interferon nebulization	Completed	11 18–75	NCT04291729
Not applicable	First Affiliated Hospital of Zhejiang University	● ASC09 with ritonavir group ● Lopinavir with ritonavir group	Not yet recruiting	180 18–75	NCT04261907
Not applicable	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	● Lopinavir with ritonavir tablets combined with xiyanping injection ● Lopinavir with ritonavir treatment	Not yet recruiting	80 18–100	NCT04295551
1, 2	University of Aarhus	● Camostat mesilate	Not yet recruiting	180 18–110	NCT04321096

into host cells. However, no approved mRNA vaccines are yet available.

An mRNA vaccine by Moderna (NCT04283461) and a vector-based vaccine (using adenovirus type 5) by CanSino Biologicals (NCT04341389) have been developed, which are passing phase I and II clinical trials to confirm their safety and efficiency. Furthermore, recombinant S-protein based vaccines conjugated with conventional adjuvants (AS03 and MF59) have advantages such as enhanced immunogenicity, requiring lower doses, and being applicable in large populations. An efficient vaccine should be able to induce adequate specific antibodies to neutralize the SARS-CoV-2 viruses. As we have learned from studies on the SARS and MERS, vaccines may be potentially associated with unwanted immune enhancement effects. Therefore, enough care should be taken before releasing any COVID-19 vaccine.

We describe below the different platforms of SARS-CoV-2 vaccines based on the WHO landscape and clinical trials.

Interestingly, children appear to suffer from a much less severe form of the SARS-CoV-2 infection. This may be related to differences in innate immunity evident at a young age, as applies to the use of vaccines such as Bacille Calmette-Guerin (BCG) [104,105].

Various strategies have been tried by researches for this purpose. Using alive attenuated virus is one of the options. Alongside this, there are ongoing efforts to develop viral-vector and recombinant protein-based vaccines to deliver viral antigens such as spike (S) protein to antigen-presenting cells. Nucleic acid-based vaccines (viral DNA and mRNA) have also been tried. Because the viral S protein is critical for the entrance of the virus into target cells, this protein has been under attention as an optimal candidate for developing vaccines. To be efficient, a vaccine must be able to trigger the production of adequate anti-virus antibodies. Simultaneously, it should possess a low risk of complications, such as unwanted immune reactions. One potentially threatening phenomenon to be avoided is known as antibody-dependent enhancement (ADE), which can result in exaggerated uptake of viral particles. Furthermore, unprotective Th2 responses, which lead to allergic inflammatory reactions, should be kept minimal following vaccination.

6.1. Whole-virus vaccines

A whole-virus vaccine is based on a physically or chemically inactivated virion, which is the entity that causes the entire disease. The inactivated whole-virus approach offers several advantages, including a good safety profile, cost-effective production, high productivity, and no need for genetic modification [95,106]. An inactivated SARS-CoV vaccine is probably the easiest and most practical for developing a coronavirus vaccine by analogy with available vaccines, including rabies and polio vaccines [107]. Whole vaccines may be more reactogenic to confer protective immunity against coronaviruses [108]. One investigation used an inactivated coronavirus (performed with formaldehyde after preparation in Vero cells) that was intramuscularly injected into rhesus monkeys to promote protective immunity. After three weeks, this vaccine preferentially induced Th1-type inflammatory responses,

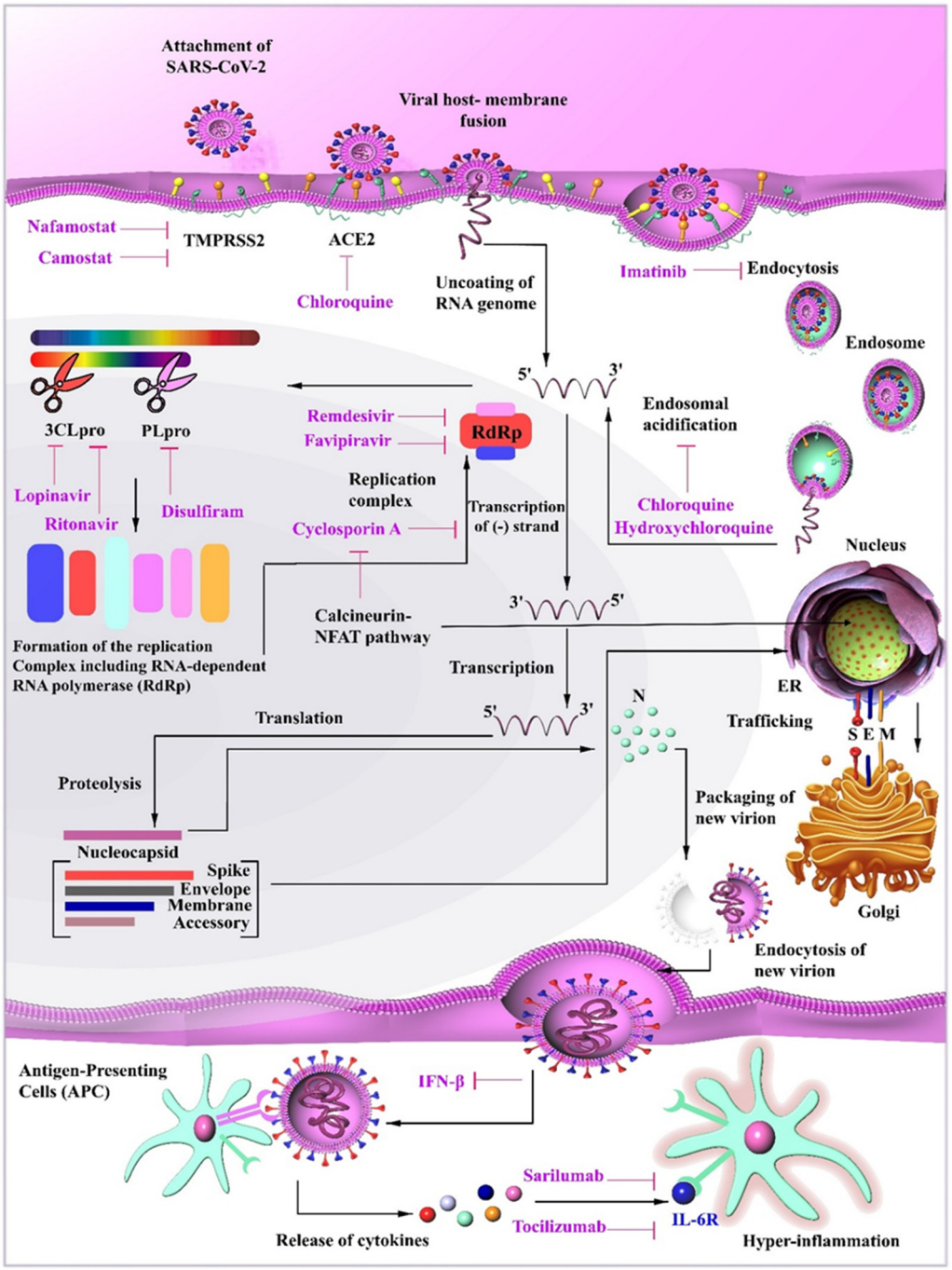

Fig. 6. Mechanisms of various drugs proposed to combat SARS-CoV-2 infection. Chloroquine inhibits the attachment of the virus to its receptor ACE2. Nafamostat and Camostat interfere with membrane fusion, which employs TMPRSS2 on the cell surface. Imatinib suppresses endocytosis and hydroxychloroquine induces degeneration of virus-containing endosomes. Remdesivir, Favipiravir, and Cyclosporin A interfere with the replication of the viral genome. Other drugs (Lopinavir, Ritonavir, and Disulfiram) suppress the formation of peptides needed for assembly of virus replicatory machine (RdRp) by deactivating viral proteases (3CLpro and PLpro). Finally, Sarilumab and Tocilizumab mitigate hyper-inflammatory responses by suppressing IL-6 interaction with its receptor and inhibiting signaling pathways.

in addition to other beneficial cellular immune responses [107]. Moreover, a live-attenuated virus vaccine is generated by a variety of techniques to significantly reduce the virulence of a virus while retaining its immunogenicity. Compared with inactivated whole-virus vaccines, live-attenuated virus vaccines can stimulate an adaptive long-term immune response. However, higher immunogenicity is usually associated with a lower safety profile [109,110]. So far, one inactivated virus and five live attenuated whole-virus vaccines, prepared by different developers, have progressed into human pre-clinical trials. Potential whole-virus vaccine candidates against SAR-CoV-2 are summarized in Table 4.

6.2. Viral vector-based vaccines

Multiple vector-based vaccines are in clinical and preclinical trials for developing potential immunity against SARS-CoV-2, and these vaccines could likely be an important tool to control the new coronavirus. These vectors are regarded as powerful tools for vaccination and for gene therapy. In general, their advantages include highly specific delivery of genes to target cells, high-efficiency gene transduction, and induction of robust cellular and humoral responses [111]. Replicating and non-replicating forms of viral vectors that are available include

Table 3
Vaccine candidates in clinical trials against SARS-CoV-2.

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
1	Shenzhen Geno-Immune Medical Institute	● Pathogen-specific aAPC	Recruiting	100 6 months to 80 years	NCT04299724
3	Murdoch Childrens Research Institute	● BCG vaccine	Recruiting	4170 ≤18	NCT04327206
1, 2	University of Oxford	● ChAdOx1 nCoV-19	Recruiting	510 18–55	NCT04324606
1	CanSino Biologics Inc.	● Recombinant novel coronavirus vaccine (adenovirus type 5 vector)	Active, not recruiting	108 18–60	NCT04313127
1	National Institute of Allergy and Infectious Diseases (NIAID)	● mRNA-1273	Recruiting	45 18–55	NCT04283461
1, 2	Shenzhen Geno-Immune Medical Institute	● Injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs	Recruiting	100 6 months to 80 years	NCT04276896
1, 2	Shenzhen Geno-Immune Medical Institute	● Injection and infusion of LV-SMENP-DC vaccine and antigen-specific CTLs	Recruiting	100 6 months to 80 years	NCT04276896

adenoviruses and poxviruses [112]. Zhao et al. found that immunization with a nucleocapsid (N) protein-based vaccine protected mice from this coronavirus through activation of CD^{4+} T IFN-γ- and cell-dependent immunity [113]. Furthermore, the modified viral vector Ankara was modified to encode the MERS-CoV S protein, and induced CD^{8+} T cell responses and neutralizing antibodies in pre-clinical studies [114]. The third type of viral vector-based vaccines is adenoviruses, and immunization of mice with a vector expressing S/N proteins led to the production of antibodies [115]. In addition, both Ad5- and Ad41-MERS-CoV S vaccines were shown to induce immune responses in mice [116]. By profiting from lessons learned in previous coronavirus vaccines, vaccine scientists have been working on developing SAR-CoV-2 vaccines within the shortest time frame possible [117]. A number of viral vector-based vaccines have progressed into human pre-clinical trials. The viral vector-based platforms used in SARS-CoV-2 vaccine studies are summarized in Table 4.

6.3. Nucleic acid vaccines

Several nucleic acid-based vaccines for coronavirus have been reported to date. Nucleic acid-based vaccines combine the positive attributes of both subunit vaccines and live-attenuated vaccines, and there has been substantial research into this type of vaccine for diverse diseases, over the last three decades [118]. These vaccines involve direct immunization through the delivery of DNA or RNA sequences encoding the antigen, and have as their main advantages, their purity and the simplicity by which this type of vaccine can be produced [119,120]. In addition, nucleic acid-based vaccines can be manufactured rapidly on a large scale and are relatively low-cost [95,121]. Furthermore, the use of these vaccines that combine the benefits of subunit and inactivated vaccines has been a critical advance [122]. The enhanced humoral and cellular immune response against SARS-CoV were elicited by a DNA-based vaccine encoding S protein, or the S1 fragment. This vaccine induced T-cell responses, as well as neutralizing antibodies [115]. Similarly, a nucleic acid-based vaccine encoding the S protein or the shorter S1 fragment, was developed for MERS-CoV. pVax1™ is a nucleic acid-based vaccine against MERS-CoV, that encodes the S protein plus an IgE leader sequence and a codon to promote expression and mRNA export [123]. Another nucleic acid-based vaccine encoding a full-length S protein against MERS-CoV strain England1, used intramuscular administration and induced neutralizing antibodies in rhesus monkeys [124]. Currently, the safety and immunogenicity of coronavirus nucleic acid-based vaccines are being evaluated in clinical trials. There are a few nucleic acid-based vaccines in the pipeline against SARS-CoV-2 in pre-clinical and clinical trials. For example, an mRNA-based vaccine against SARS-CoV-2 (INO-4800-DNA) was prepared by the US National Institute of Allergy and Infectious Diseases (NIAID) and is currently in phase 1 clinical trials. This vaccine will soon be ready for human testing in additional clinical trials. In addition, it was reported that Stermirna Therapeutics is working to develop an mRNA-based vaccine for human studies [125]. Some potential nucleic acid vaccine candidates against SAR-CoV-2 are summarized in Table 5.

6.4. Subunit vaccines

These vaccines are produced using recombinant or synthetic virus subunits. The viral nucleocapsid (N), spike (S) or envelope (E) subunits are obtained through proteolysis or chemical hydrolysis to prepare the subunit vaccines. By using one viral protein subunit, this type of vaccine activates an immune response without inducing

Table 4
Recently whole-virus-based vaccine and viral vector-based vaccine candidates against SARS-CoV-2.

Developer	Platform	Type of candidate vaccine	Current stage
Sinovac	Inactivated	Formaldehyde inactivated with alum	Pre-clinical
Codagenix/Serum Institute of India	Live attenuated virus	Deoptimized live attenuated vaccines	Pre-clinical
Codagenix/Serum Institute of India	Live attenuated virus	Deoptimized live attenuated vaccines	Pre-clinical
GeoVax/BravoVax	Non-replicating viral vector	MVA encoded VLP	Pre-clinical
Janssen Pharmaceutical Companies	Non-replicating viral vector	Ad26 (alone or with MVA boost)	Pre-clinical
University of Oxford	Non-replicating viral vector	ChAdOx1	Pre-clinical
Altimmune	Non-replicating viral vector	Adenovirus-based NasoVAX	Pre-clinical
Greffex	Non-replicating viral vector	Ad5 S (GREVAX™ platform)	Pre-clinical
Vaxart	Non-replicating viral vector	Oral vaccine platform	Pre-clinical
CanSino Biologics	Non-replicating viral vector	Viral-vectored based	Pre-clinical
Zydus Cadila	Replicating viral vector	Measles vector	Pre-clinical
Institute Pasteur	Replicating viral vector	Measles vector	Pre-clinical
Tonix Pharma/Southern Research	Replicating viral vector	Horse-pox vector	Pre-clinical

Table 5
Recently nucleic acid vaccine candidates against SARS-CoV-2.

Developer	Platform	Type of candidate vaccine	Current stage
Inovio Pharmaceuticals	DNA	DNA plasmid vaccine electroporation device	Pre-clinical
Takis/Applied DNA Sciences/Evvivax	DNA	DNA	Pre-clinical
Zydus Cadila	DNA	DNA plasmid vaccine	Pre-clinical
Fudan University/Shanghai JiaoTong University/RNACure Biopharma	RNA	LNP-encapsulated mRNA cocktail encoding VLP	Pre-clinical
Fudan University/Shanghai JiaoTong University/RNACure Biopharma	RNA	LNP-encapsulated mRNA encoding RBD	Pre-clinical
China CDC/Tongji University/Stermina	RNA	mRNA	Pre-clinical
Moderna/NIAID	RNA	LNP-encapsulated mRNA	Phase 1
Arcturus/Duke-NUS	RNA	mRNA	Pre-clinical
Imperial College London	RNA	saRNA	Pre-clinical
Curevac	RNA	mRNA	Pre-clinical

the production of antibodies against unrelated antigens [110]. Although these vaccine platforms have the highest safety profile among all other platforms, they have been considered to be weakly immunogenic [126].

Subunit vaccines are of great interest in the treatment and prevention of coronavirus diseases. Several subunit vaccines have been introduced against coronavirus targeting the S glycoprotein. Of note, the full-length S protein or its fragments, including RBD, NTD, S1 subunit, and S2 subunit, can be used as immunogens for the development of these vaccines against coronaviruses [127]. For example, a polypeptide of the SARS-CoV S glycoprotein has been successfully expressed in baculovirus vectors [128]. The recombinant protein was purified and infused into mice using Ribi or saponin as an adjuvant, and induced higher antibody titers and better protection against SARS-CoV [129]. Modified Ankara virus vaccines were developed to express the full length S protein [130]. RBD in the S1 subunit comprises the critical neutralizing fragment of MERS-CoV S protein without the non-neutralizing immunodominant domain. This type of subunit vaccine is limited to producing RBD-dependent immune responses, and these vaccines are unable to induce harmful nonspecific antibodies [95,124,131]. A sequence engineered RBD-based vaccine allowed the production of three-fold greater neutralizing antibody titers [132,133]. The N protein may provide an ideal target for the development of vaccines against coronavirus. Of note, the N protein cannot elicit antibodies to block the interaction of the virus with host cells and subsequently neutralize viral infection. Nevertheless, it may still induce cellular immune responses and specific antibodies [134,135]. M protein is a major structural protein, which could serve as a potential target for the development of subunit vaccines. In fact, SARS-CoV M subunits have high immunogenicity and can trigger high-titer antibody responses [136]. Several subunit vaccines against SAR-CoV-2 have progressed into human pre-clinical trials. Potential subunit vaccine candidates against SAR-CoV-2 are summarized in Table 6.

7. Passive immunotherapy for SARS-CoV-2

Our current knowledge of specific immune reactions against the novel SARS-CoV-2 is mainly based on previous findings with similar viruses like MERS-CoV [101]. In this regard, it is assumed that pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) will play a central role in sensing viral RNA or its replication intermediates. Within the alveolar epithelium, endosomal single-stranded (ss)RNA, TLR7/8, and the cytosolic double-stranded (ds) RNA sensor; RIG-I/MDA-5, seem to be first PRRs that detect the virus particles. After recognition of the virus by these sensors, MyD88 and MAVS adaptor proteins are activated, which subsequently induce IRF3/7 and NF-κB transcription factors. As a result, the expression of type I interferons (IFN-α and IFN-β) and proinflammatory cytokines (e.g., IL-6 and TNF-α) is increased [137]. On the other hand, the secretion of the inflammatory mediator IL-1β, and the induction of pyroptosis (an inflammatory form of cell death) mediated by the NLRP3 inflammasome, aggravate the inflammatory process. Indeed, the E and 3a proteins derived from the SARS-CoV-2 are involved in the induction of the NLRP3 inflammasome [138]. Our understanding of the recognition mechanisms of the SARS-CoV-2 is still incomplete (Fig. 8).

Immunotherapy potentially overcomes one problem of SARS-CoV-2 treatment. Various host factors in the human immune system are responsible for SARS-CoV-2 progression or regression. Immunotherapy is defined as a therapeutic intervention that targets or manipulates these immune system factors [139]. Numerous investigations have shown that increased amounts of inflammatory factors are associated with pulmonary inflammation and subsequent lung damage, first in SARS-CoV patients [140], next in MERS-CoV infections, and most recently in SARS-CoV-2. These factors include MIP-1A, G-CSF TNFα, MCP-1, IL-7, IL-10, IL-2, and IP-10 [141]. This so-called "cytokine storm" can initiate inflammation-induced lung injury and cause viral sepsis, which leads to acute respiratory distress syndrome (ARDS), respiratory failure, pneumonitis, organ failure, and potentially death [117]. Furthermore, severe cases of SARS-CoV-2 tend to have lower lymphocyte counts, higher leukocyte counts, and an altered neutrophil-lymphocyte-ratio, as well as smaller percentages of eosinophils, basophils, and monocytes. In contrast, the number of both helper T cells and suppressor T cells is significantly decreased in severe cases. However, the percentage of memory helper T cells is reduced, and that of

Table 6
Recent subunit-based vaccine candidates against SARS-CoV-2.

Developer	Platform	Type of candidate vaccine	Current stage
ExpreS2ion	Protein subunit	Drosophila S2 insect cell expression system VLPs	Pre-clinical
WRAIR/USAMRIID	Protein subunit	S protein	Pre-clinical
Clover Biopharmaceuticals Inc./GSK	Protein subunit	S-Trimer	Pre-clinical
Vaxil Bio	Protein subunit	Peptide	Pre-clinical
AJ Vaccines	Protein subunit	S protein	Pre-clinical
Generex/EpiVax	Protein subunit	Ii-Key peptide	Pre-clinical
EpiVax/Univ. of Georgia	Protein subunit	S protein	Pre-clinical
Sanofi Pasteur	Protein subunit	S protein (baculovirus production)	Pre-clinical
Novavax	Protein subunit	Full length S trimers/nanoparticle with Matrix M	Pre-clinical
Heat Biologics/Univ. Of Miami	Protein subunit	gp-96 backbone	Pre-clinical
University of Queensland/GSK	Protein subunit	S protein clamp	Pre-clinical
Baylor College of Medicine	Protein subunit	S1 or RBD protein	Pre-clinical
iBio/CC-Pharming	Protein subunit	Subunit protein, plant produced	Pre-clinical

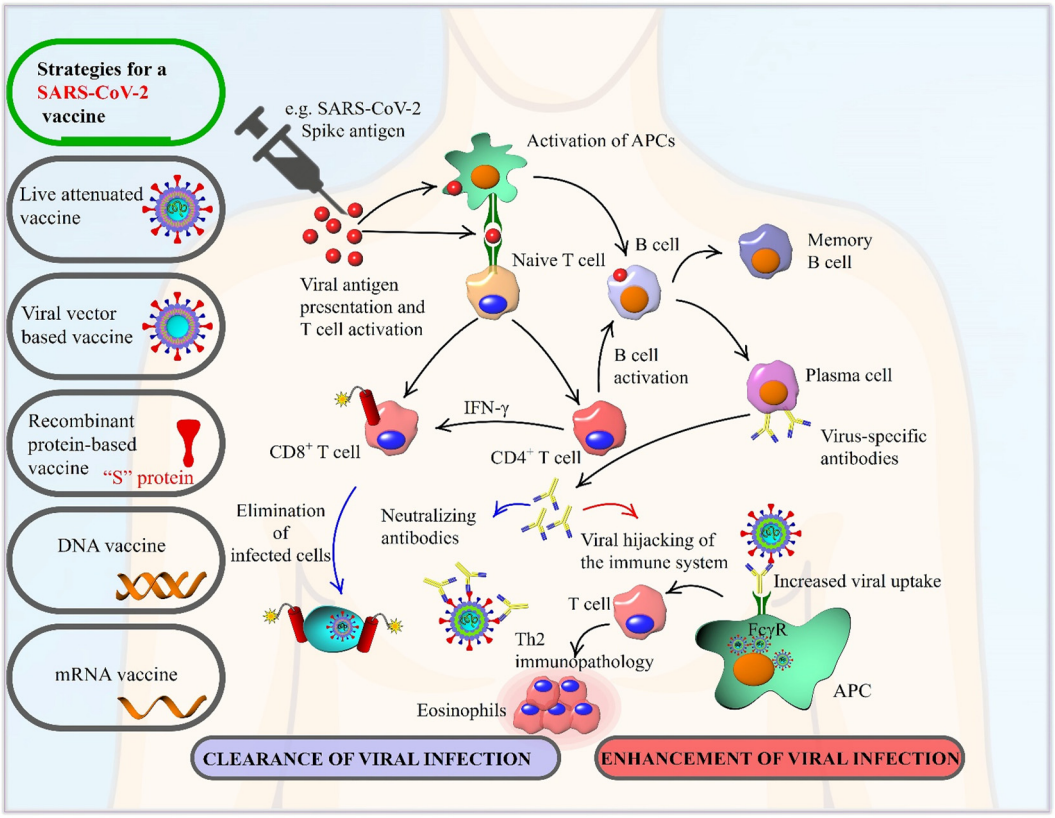

Fig. 7. Attempts for developing efficient vaccines to cope with the infection of SARS-CoV-2.

naive helper T cells is increased in severe patients. These patients also have lower levels of regulatory T cells and more noticeable lung damage in acute cases [142]. These immune responses could be modified by drugs, cytokines, monoclonal antibodies, antisera, vitamins and minerals, transplantation, and immunization.

It may be possible to treat SARS-CoV-2 patients using convalescent plasma obtained from recovered patients, and this approach is being considered for several emerging virus outbreaks. A meta-analysis of studies using convalescent plasma for managing severe acute respiratory infections suggests that the appropriate use of these products results in reduced mortality risk [143]. Convalescent plasma was used for treating SARS-CoV patients with potentially promising results. However, in the absence of suitable clinical trials, the results remain controversial [144]. In addition, Zhao et al. published results showed the therapeutic and prophylactic efficacy of camel serum-containing MERS-CoV neutralizing antibodies in reducing weight loss, viral load, and improving pulmonary function in MERS patients [145]. Recently, in a preliminary non-controlled case series of 5 severe patients, the administration of convalescent plasma collected from patients who had recovered from SARS-CoV-2 containing antibodies was followed by an improved clinical outcome [146].

Humoral immune responses to infection, especially the rapid production of neutralizing antibodies, have a protective effect against infection and prevent reinfection. Epitopes of T and B cells were extensively mapped for the main SARS-CoV proteins, N, E, S, and M protein [147]. Furthermore, previous infection with non-SARS-CoV viruses may have caused many people (including children) to already have some levels of protective antibodies against the novel virus [148,149]. For example, Shanmugaraj et al. summarized the potential neutralizing antibody-based therapeutic strategies for SARS-CoV-2 including the neutralizing antibodies against SARS-CoV (80R, CR3014, CR3022, F26G18, F26G19, m396, 1A9, 201, 68 and S230) and MERS-CoV (MERS-4, MERS-27, 4C2, m336, G4, D12, JC57-14, MERS-GD27, MERS-GD33, LCA60, MCA1, CDC2-C2, 7D10, and G2) [150]. A list of possible therapies for SARS-CoV-2 based on neutralizing antibodies, convalescent plasma, and other immunotherapies that have been tested in ongoing and completed human clinical trials, is provided in Table 7.

Exaggerated immune and inflammatory responses are considered to be responsible for the severity of symptoms and a poor clinical outcome of coronavirus infections. Interferons have shown to play a crucial role in the defense against coronavirus diseases. A less efficient interferon-mediated immune response can explain the increased mortality rates in the elderly. Earlier induction of interferons in children and their less developed immune system could be the reasons behind their zero or near to zero fatality rate. Administration of interferon-inducing agents could reduce the mortality of SARS at a very early stage of the disease. Adding interferon-γ to an interferon-I, as a synergistic combination therapy, might maximize the benefits [151]. There are currently several interferons employed in clinical settings that could provide a therapy for SARS-CoV-2. Furthermore, nitric oxide (NO) is a selective pulmonary vasodilator and holds promise as an anti-inflammatory agent [152]. NO is a critical cellular signaling molecule synthesized by nitric oxide synthase (NOS). In the pulmonary airways, NOS is present in a variety of cells, including neurons, macrophages, airway epithelial cells, and vascular endothelial cells. NOS activity is critical to mediate smooth muscle relaxation, neurotransmission, mucin secretion, and is also a well-known mediator in the cellular response to microbial infection [153]. Various inflammatory factors, such as cytokines and LPS, can induce high and sustained NO production. Inducible nitric oxide synthase activity can result in anti-inflammatory or pro-inflammatory responses, cytoprotection, or cytotoxicity, depending on the circumstances [154]. Inhaled NO results in a transient improvement in systemic oxygenation. There are no published data from trials that describe the use of pulmonary vasodilators in COVID-19 patients. However, a previous review showed ARDS treatment by inhaled NO had no significant effect on mortality and increased the likelihood of acute kidney injury [155]. Several

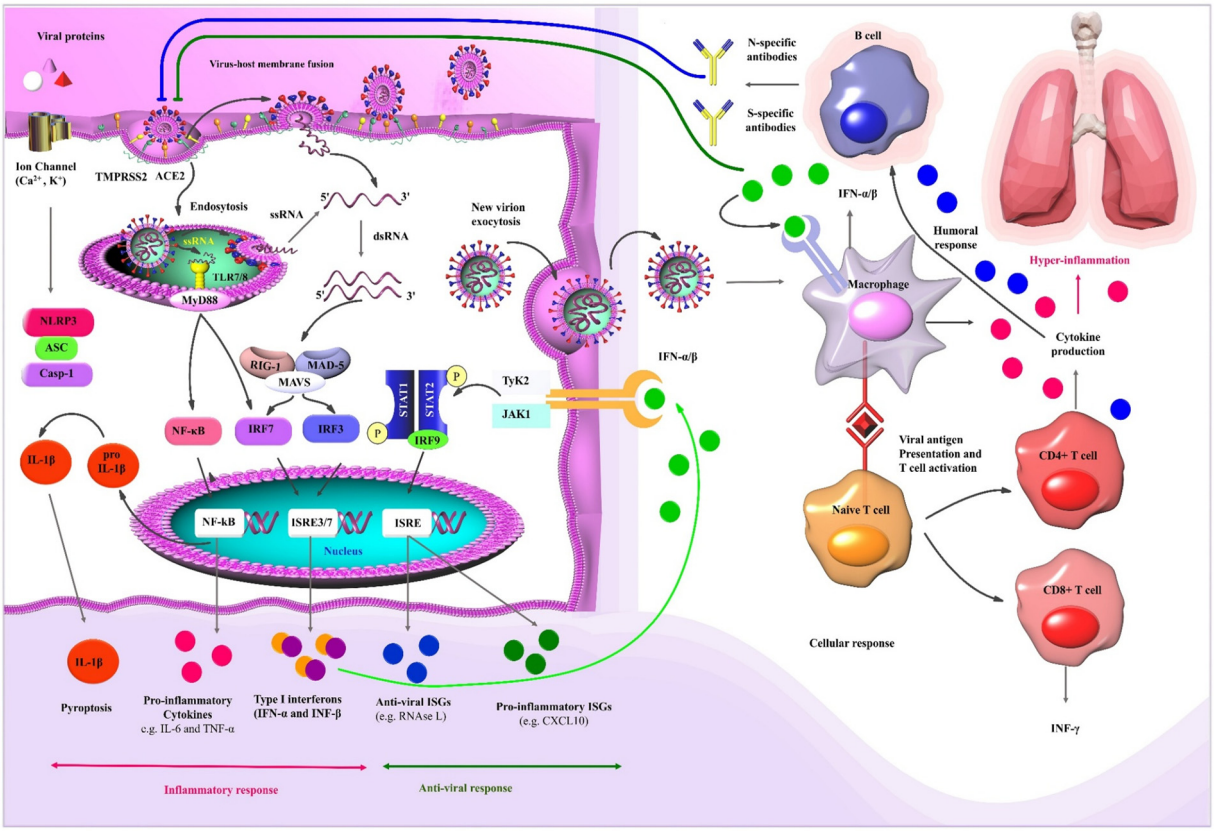

Fig. 8. Possible immune reactions induced by the SARS-CoV-2. The predictions are based on studies of SARS-CoV and MERS-CoV viruses. Non-specific recognition by innate immune receptors (e.g., RNA sensors, TLR7/8, RIG-I/MDA-5, and NLRP3 inflammasome) seems to be the first effect of the virus within alveolar epithelial cells. The main transcription factors involved in the induction of inflammatory mediators (e.g., IL-1β, IL-6, and type I IFNs) are NF-κB and IRF3/7. The antiviral activity of type I IFNs is augmented by many ISGs such as RNAse L. Cell-based immunity is based on macrophages, B cells, and T cells, which directly eliminate viral particles. However, hyper-inflammation resulting from an unbalanced action of the immune system could exacerbate COVID-19 outcomes.

clinical trials are underway to determine whether inhaled NO can improve oxygenation in SARS-CoV-2 patients (Table 6). In addition, it was proposed that treatment with statins, a multifunctional class of drugs with several potential applications, could inhibit MyD88 signaling and NF-κB response. This could inhibit inflammatory responses that would lead to ameliorated disease progression in COVID19 patients. There is evidence that down-regulation of NF-κB signaling could increase survival in mouse models of SARS-CoV infection [156,157]. A number of immunotherapies that have been proposed as a treatment for SARS-CoV-2 are currently undergoing clinical trials (Table 6).

Melatonin is a neurohormone produced by the pineal gland. This molecule has many beneficial activities, including immunomodulatory, anti-inflammatory, antioxidant properties within the body [158,159]. Because of these functions, some researchers have proposed this agent could be a therapeutic option for treating viral infections and respiratory diseases, including ARDS and acute lung injury (ALI) [160]. The mechanisms of action of melatonin (which has an excellent safety profile) include, at least in part, reducing anxiety, improving sleep, and modulating vascular permeability, which may be useful in improving prognosis of SARS-CoV-2 patients [161].

8. Cell-based therapies

ARDS is a medical condition characterized by severe uncontrolled inflammation in the lungs, which causes disturbances in the surfactant and the pulmonary capillary endothelial cells, resulting in fluid accumulation in the distal parts of the lung [162]. The beneficial effects of using mesenchymal stem cells (MSCs), including their immunomodulatory, antimicrobial, and antiapoptotic properties, have been reported in previous studies. In particular, the immunomodulatory functions of these cells are among their most relevant properties. It has been shown that although histocompatibility complex (MHC) class I molecules are expressed on human MSCs, they lack class II MHC molecules, rendering these cells hypoimmunogenic or "immune-privileged" properties. Through this property, MSCs can escape immune recognition by T helper (CD4+) lymphocytes and immune destruction by natural killer cells. MSCs can regulate the activity of both the innate and adaptive immune responses through either cell-cell interaction, secretion of trophic factors, or activation of regulatory T cells. In animal models and in vitro studies, MSCs have been shown to promote non-specific immune reactions (i.e., innate immunity) through either directly killing bacteria or engaging multiple antimicrobial mediators such as LL-37, lipocalin-2, and beta-defensin-2 via the toll-like receptor 4 signaling pathway [163]. MSCs are also capable of fighting microbial agents by activating tryptophan metabolism by increasing indoleamine 2,3-dioxygenase activity [164]. They are known to support the survival and function of neutrophils and macrophages. This activity is mediated by transforming the macrophage phenotype to the anti-inflammatory (type 2) from the pro-inflammatory (type 1). MSCs mediate many processes, including secretion of growth factors that target vascular cells, hepatocytes, neurons, and other cells, altering the balance of anti/proapoptotic genes, changing mitochondrial biology, and microvesicle transfer [165]. MSCs can trigger antiapoptotic proteins both in vivo (animal models of renal, cerebral, and cardiac injuries) and also in vitro. On the other hand, MSCs can promote autophagy, another form of programmed cell death, through the phosphoinositide 3-kinase/protein kinase B signaling pathway. This function, along with another phenomenon known as mitophagy (i.e., selective degradation of mitochondria), has been shown to be important for MSCs to carry out their protective role against oxidative damage to the lungs. Xu et al. reported the

Table 7
Passive immunotherapy for SARS-CoV-2 in clinical trials.

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
Early 1	Tongji Hospital	● Recombinant human interferon α1β	Not yet recruiting	328 ≤18	NCT04293887
2	First Affiliated Hospital of Wenzhou Medical University	● Thalidomide	Not yet recruiting	100 ≤18	NCT04273529
Not applicable	Tongji Hospital	● Tocilizumab ● Standard of care Procedure: continuous renal replacement therapy	Recruiting	120 18–80	NCT04306705
2	First Affiliated Hospital of Fujian Medical University	● Fingolimod	Recruiting	30 ≤18	NCT04280588
2, 3	Fasa University of Medical Sciences	● Levamisole pill with budesonide with formoterol inhaler ● Lopinavir with ritonavir with hydroxychloroquine	Not yet recruiting	30 18–100	NCT04331470
2	First Affiliated Hospital of Wenzhou Medical University	● Thalidomide	Not yet recruiting	40 ≤18	NCT04273581
2, 3	Qilu Hospital of Shandong University	● Bevacizumab injection	Recruiting	20 ≤18	NCT04275414
2, 3	Peking Union Medical College Hospital	● Methylprednisolone therapy ● Standard care	Recruiting	80 ≤18	NCT04244591
3	Tongji Hospital	● Sildenafil citrate tablets	Recruiting	10 ≤18	NCT04304313
4	Tongji Hospital	● Methylprednisolone	Recruiting	100 ≤18	NCT04263402
Not applicable	Beijing Chao Yang Hospital	● Methylprednisolone	Recruiting	400 ≤18	NCT04273321
–	Hudson Medical	● Eculizumab	Available	– ≤18	NCT04288713
4	University Hospital, Ghent	● Usual care ● Anakinra ● Siltuximab ● Tocilizumab	Not yet recruiting	342 18–80	NCT04330638
2	Southeast University, China	● PD-1 blocking antibody with standard treatment ● Thymosin with standard treatment ● Standard treatment	Not yet recruiting	120 ≤18	NCT04268537
Not applicable	University of Palermo	Dietary supplement: vitamin C	Recruiting	500 All	NCT04323514
Not applicable	Peking Union Medical College Hospital	● Intravenous immunoglobulin ● Standard care	Not yet recruiting	80 ≤18	NCT04261426
2	Assistance Publique - Hôpitaux de Paris	● Tocilizumab	Not yet recruiting	240 ≤18	NCT04331808
Not applicable	Shanghai Public Health Clinical Center	● Inactivated convalescent plasma	Recruiting	15 All	NCT04292340
2	Xijing Hospital	● Nitric oxide gas	Not yet recruiting	104 ≤18	NCT04290871
2	Massachusetts General Hospital	● Nitric oxide	Not yet recruiting	240 ≤18	NCT04305457
Not applicable	Foundation IRCCS San Matteo Hospital	● Hyperimmune plasma	Active, not recruiting	49 ≤18	NCT04321421
2	Southeast University, China	● PD-1 blocking antibody with standard treatment ● Thymosin with standard treatment ● Standard treatment	Not yet recruiting	120 ≤18	NCT04268537
2, 3	Regeneron Pharmaceuticals	● Sarilumab	Recruiting	400 ≤18	NCT04315298
4	Negrin University Hospital	● Dexamethasone	Not yet recruiting	200 18	NCT04325061
2	Università Politecnica delle Marche	● Tofacitinib	Not yet recruiting	50 18–65	NCT04332042
3	Assistance Publique - Hôpitaux de Paris	● Discontinuation of RAS blocker therapy ● Continuation of RAS blocker therapy	Not yet recruiting	554 ≤18	NCT04329195
3	OncoImmune, Inc.	● CD24Fc	Not yet recruiting	230 ≤18	NCT04317040
Not applicable	University Health Network, Toronto	● Ruxolitinib	Not yet recruiting	64 ≤12	NCT04331665
2	National and Kapodistrian University of Athens	● Colchicine ● Standard treatment	Not yet recruiting	180 ≤18	NCT04326790
3	Assistance Publique - Hôpitaux de Paris	● Usual practice with SYMBICORT RAPIHALER ● Usual practice	Not yet recruiting	436 18–75	NCT04331054
Not applicable	Wuhan Union Hospital	● Immunoglobulin of cured patients ● γ-Globulin	Not yet recruiting	10 ≤18	NCT04264858
3	Shanghai Jiao Tong University School of Medicine	● Recombinant human interferon alpha-1b ● Thymosin alpha 1	Recruiting	2944 18–65	NCT04320238
3	Misr University for Science and Technology	●Dietary supplement: natural honey ● Standard care	Not yet recruiting	1000 5–75	NCT04323345
1, 2	Chinese Academy of Sciences	● CAStem	Recruiting	9	NCT04331613

Table 7 (*continued*)

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
				18–70	
2	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	● Anti-SARS-CoV-2 plasma ● SARS-CoV-2 non-immune plasma	Not yet recruiting	150 ≤18	NCT04323800
2	Universidad del Rosario	● Plasma	Not yet recruiting	10 18–60	NCT04332380
3	Assistance Publique - Hôpitaux de Paris	● Naproxen ● Standard of care	Not yet recruiting	584 ≤18	NCT04325633
2, 3	Universidad del Rosario	● Plasma ● Hydroxychloroquine ● Azithromycin	Not yet recruiting	80 18–60	NCT04332835
3	Estudios Clínicos Latino América	● Colchicine ● Local standard of care	Not yet recruiting	2500 ≤18	NCT04328480
Not applicable	Mazandaran University of Medical Sciences	● Convalescent plasma	Enrolling by invitation	30 30–70	NCT04327349
2	Zhongnan Hospital	● Vitamin C ● Sterile water for injection	Recruiting	140 ≤18	NCT04264533
3	Hospital Sirio-Libanes	● Dexamethasone	Not yet recruiting	290 ≤18	NCT04327401
3	Hospital of Prato	● Baricitinib	Recruiting	60 18–80	NCT04320277
Not applicable	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	● Xiyanping injection ● Lopinavir with ritonavir, alpha-interferon nebulization	Not yet recruiting	348 18–70	NCT04275388
2, 3	University of Trieste	● Methylprednisolone ● Standard care	Recruiting	104 18–80	NCT04323592
2	Mayo Clinic	● Convalescent plasma	Not yet recruiting	20 ≤18	NCT04325672
2	Upinder Singh, Stanford University	● Peginterferon lambda-1a ● Standard of care treatment	Not yet recruiting	120 18–64	NCT04331899
3	Montreal Heart Institute	● Colchicine	Recruiting	6000 ≤40	NCT04322682
2	Lucio Manenti, Azienda Ospedaliero-Universitaria di Parma	● Colchicine	Not yet recruiting	100 18–85	NCT04322565
2	National Cancer Institute, Naples	● Tocilizumab injection	Recruiting	330 All	NCT04317092
3	Hoffmann-La Roche	● Tocilizumab (TCZ)	Not yet recruiting	330 ≤18	NCT04320615
2	Università Politecnica delle Marche	● Tocilizumab	Not yet recruiting	30 18–90	NCT04315480
1	Hospital San Jose Tec de Monterrey	● Convalescent plasma	Not yet recruiting	20 ≤18	NCT04333355
2	Massachusetts General Hospital	● Nitric oxide gas	Recruiting	220 18–99	NCT04306393
Not applicable	Beijing 302 Hospital	● Conventional medicines and traditional Chinese medicines granules ● Conventional medicines and lopinavir with ritonavir	Not Applicable	150 14–80	NCT04251871
2	Frederiksberg University Hospital	● RoActemra iv ● RoActemra sc ● Kevzara sc ● Standard medical care	Not yet recruiting	200 ≤18	NCT04322773
2, 3	Assistance Publique - Hôpitaux de Paris	● Sarilumab	Recruiting	240 ≤18	NCT04324073
2	University of British Columbia	● Nitric oxide 0.5% with nitrogen 99.5% gas for inhalation	Active, not recruiting	20 ≤14	NCT03331445
3	Université de Sherbrooke	● Vitamin C ● Control	Recruiting	800 ≤18	NCT03680274
2, 3	Swedish Orphan Biovitrum	● Emapalumab ● Anakinra	Not yet recruiting	54 30–79	NCT04324021

pathological characteristics of a biopsy sample obtained at autopsy from a SARS-CoV-2 patient with severe ARDS [166]. Unfortunately, age-related loss of the capacity of the lung tissue to self-repair may explain the progressive age-related mortality reported in older SARS patients with ARDS [167,168]. No therapeutic drugs have yet been approved for the treatment of ARDS [169]. Hence, current treatment strategies are mainly based on supportive care, such as prone positioning, conservative fluid replacement, and lung-protective ventilation [170]. Therefore, the utilization of stem cells in experimental protocols may be considered for coronavirus diseases, including SARS, MERS, and SARS-CoV-2 in human medicine.

Cell-based therapies, especially stem cells, could have both curative and preventive potential in COVID19. Cell-based therapies may be an innovative treatment for ARDS through several pathways that may augment recovery from lung injury and reduce the magnitude of lung damage [171]. Several types of stem cells have been considered for clinical use, such as cord blood mesenchymal stem cells (CBMSCs) [172], umbilical cord mesenchymal stem cells (HUCMSCs) [172,173], umbilical cord Wharton's Jelly derived-mesenchymal stem cells (UCWJDMSCs) [174], umbilical cord-derived mesenchymal stem cells (UCMSCs) [175], umbilical cord blood mononuclear cells (UCBMCs) [176], and human menstrual blood-derived stem cells (HMBSCs)

[177]. MSC-based treatment could help ARDS through inhibition of collagen accumulation, reducing alveolar cell apoptosis, and preventing the collapse of lung airways. Some of the most attractive properties of MSCs are the ability to modulate immune responses, antimicrobial properties, anti-apoptotic effects, and robust regenerative potential (Fig. 9). It remains highly controversial as to which of several MSC mediators are involved in the therapeutic response [178]. MSC secreted factor candidates for ARDS treatment, include angiopoietin-1 [179], hepatocyte growth factor (HGF) [180], keratinocyte growth factor (KGF) [181], insulin growth factor (IGF) [182], interleukin 1 receptor antagonist (IL-1RN) [183], interleukin 10 (IL-10) [184], interleukin 6 (IL-6), tumor necrosis factor-stimulated gene 6 (TSG-6) [185], lipoxin A4 [186], prostaglandin E2 (PGE2) [175], lipocalin-2 [187], β-defensin-2 [188], stanniocalcin-1a [189] and extracellular vesicles [190]. Recent studies have suggested that there is a direct correlation between the regulation of these bioactive factors after engraftment of MSCs in the lungs after ARDS [178]. In summary, a large body of preclinical and clinical evidence is accumulating on the use of MSCs for the treatment of ARDS.

Stem cell therapy, especially MSCs, has been shown to reduce pulmonary inflammation and affect pulmonary tissue regeneration. Therefore, it is investigated in ARDS patients. Wilson et al. found that the administration of allogeneic MSCs to ARDS patients resulted in no prespecified adverse events, including ventricular tachycardia, hypoxemia, and cardiac arrhythmia [191]. Recently, results from Chen et al. suggested that MSCs could notably improve the survival rate of influenza virus subtype H7N9-induced ARDS, which provides a theoretical basis for the treatment of ARDS patients [192]. Of note, coronavirus-induced ARDS shares similar complications and corresponding organ failure to influenza H7N9, so MSCs therapy could be a possible alternative for treating COVID19 patients. Clinical and pre-clinical trials conducted in China have demonstrated that MSCs are naturally resistant to SARS-CoV-2 infection, and transplantation of these cells could improve the outcome in SARS-CoV-2 patients. For instance, Leng et al. investigated whether MSC transplantation affected the outcome of SARS-CoV-2 patients in Beijing Youan Hospital, China. The results showed that MSC therapy could remarkably improve the outcome of SARS-CoV-2 patients without any adverse events (Fig. 10). After MSC therapy, the C-reactive protein (CRP) levels decreased, the peripheral blood lymphocytes were increased, and the over-activated cytokine-secreting immune cells $CXCR^{3+}$ CD^{8+} T cells and $CXCR^{3+}$ NK cells $CXCR^{3+}$ CD^{4+} T cells disappeared within one week. Moreover, the level of IL-10 increased, while plasma inflammatory factor TNF-α was significantly decreased compared to the control group. Furthermore, MSCs do not express TMPRSS2 and ACE2, explaining why MSCs are resistant to infection by SARS-CoV-2 [193]. Although various clinical trials have been commenced to test the effects of MSCs in severe SARS-CoV-2 patients, convincing positive results have yet to be reported. The upcoming clinical trials to evaluate the safety and effectiveness of MSCs for the treatment of SARS-CoV-2 patients are summarized in Table 8.

9. The emergence of nanomedicine as a new therapeutic strategy in SARS-CoV-2 treatment

Treatment of pulmonary infectious diseases using nanoparticles has recently attracted significant attention [194,195]. Small molecule drugs have disadvantages such as lack of targeting to lungs, difficulties with stability during storage and administration, and considerable expense [196,197]. Upon reaching the lungs, drugs may be enzymatically degraded by pulmonary enzymes. In addition, the pulmonary airways are a mucus-covered epithelial bed, which can act as a barrier preventing the penetration of drugs into the lungs [198]. However, therapeutic nanoparticles may act as an alternative delivery platform to the lungs, depending on physiological parameters (respiratory rate and lung volume) and the pathophysiological state (disease nature). Considering the particle size, the target tissue, and respiratory rate, various mechanisms can be employed to deliver therapeutic agents into the lungs. In the pulmonary alveoli, the clearance rate of particles is mainly determined by the size [199]. Furthermore, vaccines must be equipped with efficient molecules (i.e., new generation composite vaccines) to potentiate their immunogenic and adjuvant activities [200]. To address some of these issues, nano-delivery platforms could provide a viable option as they are designed to allow protection against biological degradation, better stability, and higher efficiency (synergistic effects) [201,202], to improve the effectiveness of therapeutic agents [203]. Therefore, nanoparticles (NPs) are being investigated as carriers for targeting drugs to treat a variety of pulmonary infectious diseases.

To develop effective vaccines for coronavirus diseases (in particular the novel COVID-19), we can use NPs as targeted carriers. Furthermore, NPs have the potential to be employed to develop therapeutic and diagnostic (i.e., biosensor) systems. Recent global pandemics caused by coronaviruses (SARS-CoV, MERS-CoV, and now COVID-19) have underlined the necessity of rapidly developing effective vaccines. Using a novel procedure involving protein-protein micellar NPs, Coleman et al. produced an adjuvant-conjugated vaccine against SARS-CoV S and MERS-CoV S proteins. These researchers used first cultured Baculovirus insect cells to produce the complete S protein, which was then self-assembled into NPs. For potentiating the production of neutralizing antibodies by immune cells, they used adjuvants (aluminum hydroxide (alum) or Matrix M1) [204]. Anti-MERS-CoV immunoglobulins (recognizing MERS-CoV S protein) were detected in the mice treated with MERS-CoV S NPs. The immune response was augmented by using the Matrix-M1 adjuvant triggering the high production of anti-S neutralizing antibody conferring immune protection against MERS-CoV infection in mice [205]. Jung et al. also produced a NP based vaccine with the MERS-CoV S protein gene (Ad5/MERS) and MERS S protein, using a heterologous prime-boost immunization strategy. They used a recombinant adenovirus serotype 5 to conjugate the antigens to the NPs. The vaccines were proved to be able to activate Th1/Th2 lymphocytes in an appropriate ratio [206]. In another study, Roh et al. used a combination of SARS-CoV N protein inhibitors and NP-based RNA oligonucleotides to develop a vaccine against the virus. By applying RNA oligonucleotide conjugated to QDs on a biochip, they showed that the SARS-CoV N protein was effectively suppressed by (−)-catechin gallate and (−)-gallocatechin gallate through a dose-dependent attenuation of its binding affinity [207].

Biosensors are used to detect and quantify biological responses and are now widely used in medical diagnostic procedures as point-of-care instruments [208,209]. Biosensor-based systems are effective, simple, reliable, and relatively inexpensive platforms that can be used in clinical settings. Using these systems, the sensitivity and reproducibility of clinical analysis can be maximized [210,211]. Nanobiosensors were first applied to detect antibody mimicking proteins (AMPs) by Ishikawa et al. who configured In_2O_3 nanowire based-biosensors with an antimicrobial peptide (fibronectin, Fn). Using bovine serum albumin (44 μM) as the control, this system was able to detect sub-nanomolar levels of SARS-CoV nucleocapsid (N) protein [212]. In addition, point-of-care fluorescent and colorimetric systems have been designed to detect DNA and RNA molecules, especially in less equipped laboratories. In this regard, MERS-CoV DNA was successfully detected using a colorimetric assay (AgNPs were served as a colorimetric agent). In this assay, the viral DNA was detected based on acpcPNA-induced NP aggregation, which was highly sensitive, and did not bind non-complementary nucleic acids (either single, two, or full-length mismatch) [213]. Moreover, Kim et al. developed a colorimetric-based method which was able to detect MERS-CoV DNA (length of 30 bp) as low as 1 pmol/μL using self-complementary double-stranded DNA (dsDNA) shielded with gold NPs [214]. These medical diagnostic strategies could provide cheap and disposable alternatives to detect and screen for the presence of coronaviruses.

Because NPs-based vaccines can effectively trigger the humoral immune response and act as a versatile antigen-presenting system, they

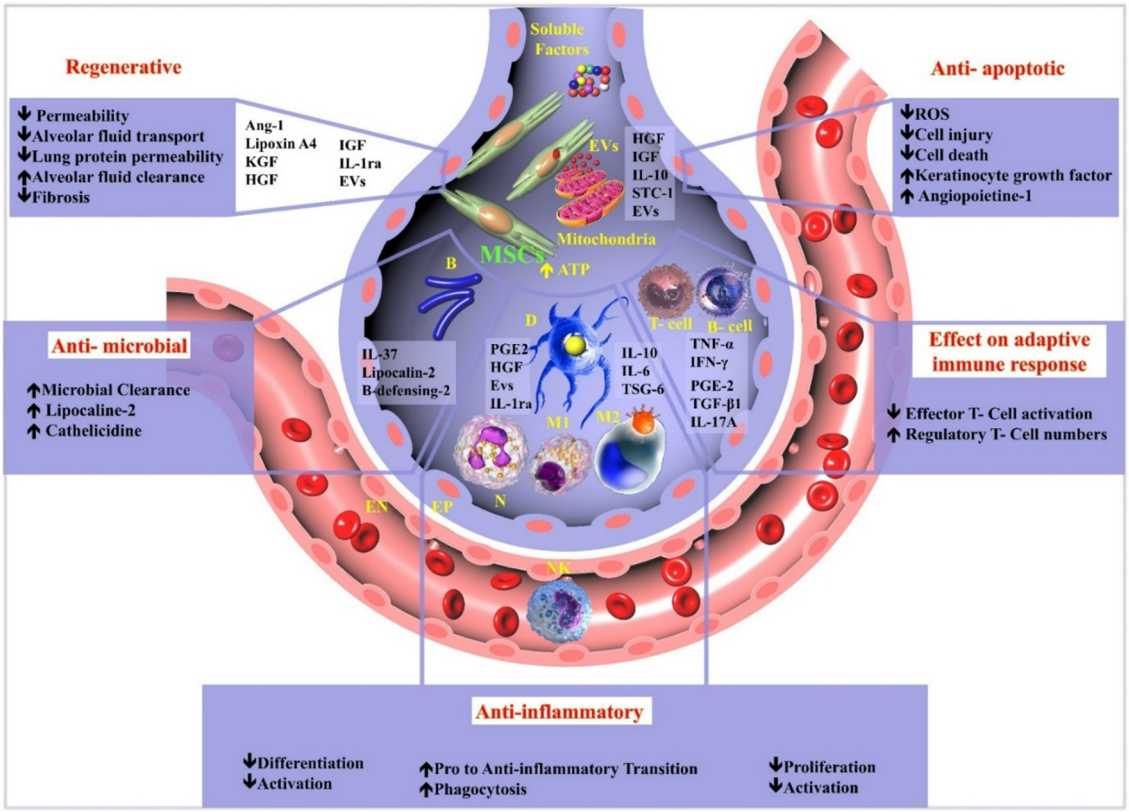

Fig. 9. The therapeutic effects of MSCs and their secreted factors for SARS-CoV-2-related ARDS. The diverse immunological and biological function of mesenchymal stem cells. MSCs promote anti-apoptotic effects mainly by inducing growth factors and directly or indirectly reducing factors that damage cells (ROS, etc.). A primary function of MSCs is to modulate immune responses by activating effector T cells (either CD4+ or CD8+) and regulating the function and proliferation of regulatory T (Tregs) cells. MSCs also affect cellular adaptors of the innate immune response (mainly neutrophils and macrophages). In particular, in response to induction by MSCs, macrophages are phenotypically transformed from a pro- to anti-inflammatory state. All immunomodulatory functions of MSCs finally result in a potent anti-microbial response resulting in microbial clearance in part by activation of lipocaline-2 and cathelicidin. By inducing the secretion of a variety of growth factors, MSCs can potentiate the regeneration of pulmonary alveoli and reduce lung fibrosis. Molecular adaptors of these effects of MSCs are shown. MSCs: mesenchymal stem cells; M1 and M2: M1 and M2 macrophages; B: bacteria; N: neutrophil; D: dendritic cell; NK: natural killer cell; EP: epithelial cell; EN: endothelial cell; EVs: extracellular vesicles; PGE2: prostaglandin E2; HGF: hepatocyte growth factor; IL-1ra: interleukin 1 receptor antagonist; IL-10: interleukin 10; IL-6: interleukin 6; TSG-6: tumor necrosis factor-inducible gene 6 protein; IGF: insulin growth factor; STC-1: stanniocalcin 1; Ang-1: angiopoietin 1; KGF: keratinocyte growth factor; ROS: reactive oxygen species.

can be effectively used to increase immunity against the viruses that cause acute respiratory syndromes [215]. Vaccines that have been developed using mRNAs benefit from advantages, such as mimicking natural infection and triggering a more potent immune response. In addition, there is a possibility to incorporate multiple mRNAs into a single vaccine. The SARS-CoV-2 S protein (140 kDa) is a peptide with 1273 residues [216], and its respective mRNA has been employed to develop an effective vaccine. In this approach, liquid NPs and chemical modification were used to stabilize an injectable form of the mRNA-based vaccine using soluble nanoparticles. This lipid nanoparticle (LNP)-encapsulated mRNA vaccine is being tested in Phase 1 clinical trial (NCT04283461) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) in the US. This novel vaccine was designed by Moderna in collaboration with investigators at the NIAID Vaccine Research Center to identify an antigen linked to the SARS-CoV-2 prefusion-stabilized S protein [217]. In February 2020, the Novavax Company, which had already worked on MERS and SARS, also announced the start of animal studies on potential candidates to produce a SARS-CoV-2 vaccine. They used SARS-CoV-2 derived S protein along with Matrix-M adjuvant in a recombinant nanoparticle technology [217]. A trial for the efficacy of adipose mesenchymal stem cell-derived exosomes (MSCs-Exo) (through inhalation of an aerosol) in the treatment of severely ill patients with SARS-CoV-2 infection is underway (NCT04276987). These exosomes are known to mitigate lung inflammation and reduce injury in various pathological conditions, as well as to increase the phagocytic activity and killing potency of macrophages.

10. Concluding remarks

This review has provided an overview of therapeutic agents designed to target SARS-CoV-2 based on an extensive search of ClinicalTrials.gov and medical databases, with a focus on clinical trials. Considering the rapid progression of research in this field, it will be difficult to remain completely up to date. However, the effectiveness of the most recent clinical trials have been collected and potential research areas have been proposed to extend the range of therapeutic candidates against SARS-CoV-2. Most antiviral strategies against SARS-CoV-2, which have been studied in pre-clinical and clinical trials, are already used medicines against other RNA viruses, such as SARS-CoV, MERS-CoV, influenza, HCV, and Ebola. In addition, this review has also included an overview of SARS-CoV-2 biology and antiviral therapies that have exploited several nanoscale agents were explored. Nanomedicine-based therapies (bioengineered and vectored antibodies, cytokines, and vaccines) have shown some promise for the treatment of SARS-CoV-2 infections. We further discussed the complex cellular interactions responsible for SARS-CoV-2 cell entry and replication, as well as drugs that can target these pathways. Vaccine platforms, passive immunotherapy, and cell-based therapies were also covered.

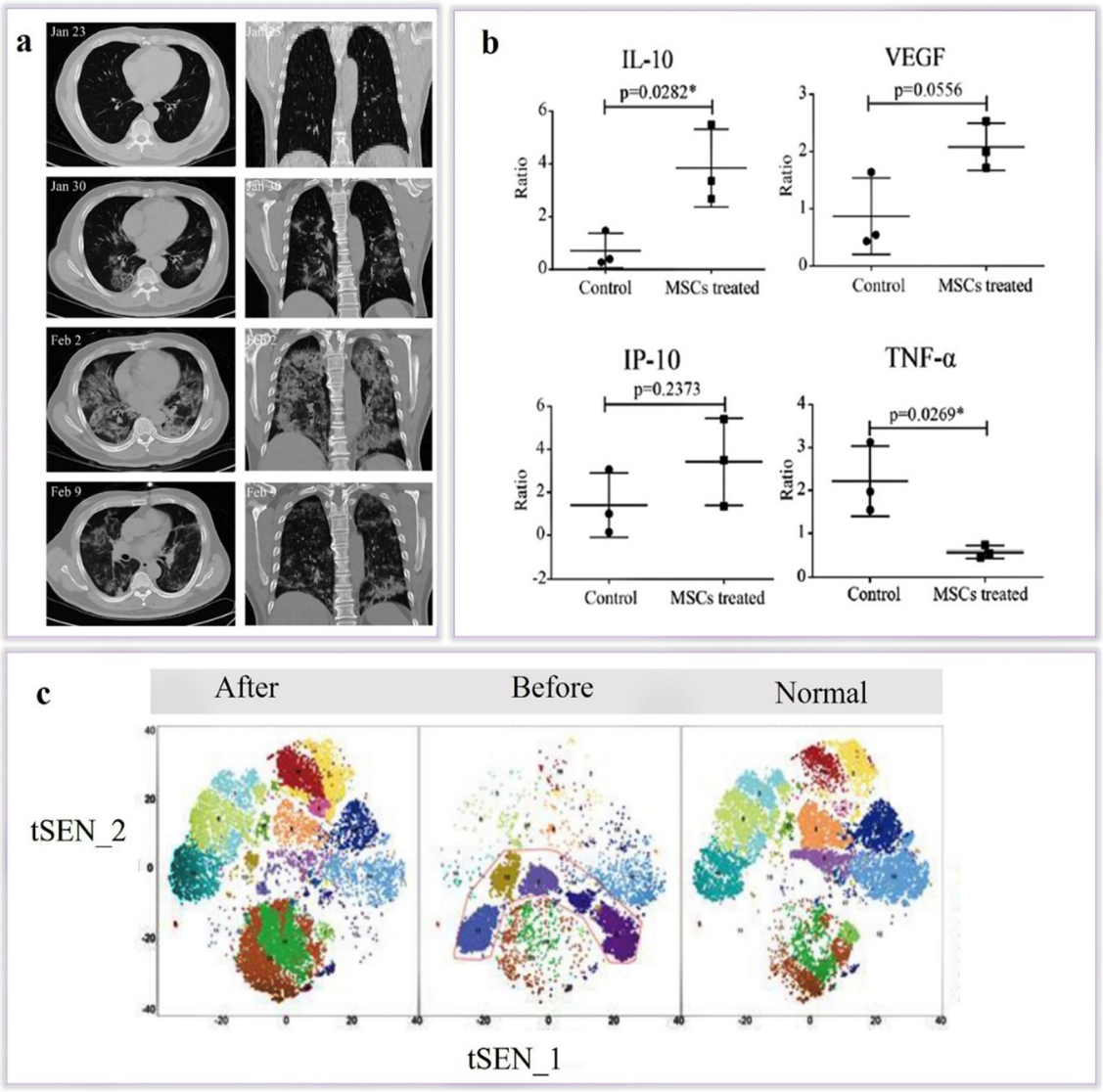

Fig. 10. MSCs improve the outcome of SARS-CoV-2 patients with ARDS. a) Chest computed tomography images of the severe SARS-CoV-2 patient. b) The pattern of serum cytokine/chemokine/growth factors. c) The profile of the over-activated NK cells and T cells of SARS-CoV-2 patients.
Reproduced with permission from [193].

Currently in use or investigational agents for SARS-CoV-2 target either the virus or host-derived molecules (e.g., interferons, glucocorticoids). The combination of lopinavir and ritonavir might treat the specific virus, and SARS-CoV-2 receptor inhibitors may be helpful in reducing lung cell viral entry and improve lung function in COVID19 patients. Some patients infected with SARS-CoV-2 were significantly improved after treatment with the lopinavir in combination with ritonavir. However, other case reports showed that treatment with lopinavir and ritonavir did not significantly alleviate SARS-CoV-2 related pneumonia [218]. Although there were no reports of acute respiratory failure in these patients, it is questionable whether this was solely related to the antiviral drugs or not [69]. Regardless, lopinavir plus ritonavir is still considered a viable treatment for SARS-CoV-2 infection. Cell entry-based therapeutics, such as chloroquine, hydroxychloroquine, anti-ACE2, and anti-CD147 antibodies could also guide us towards the discovery of new treatments for SARS-CoV-2 infection. These therapeutic modalities could also be useful to reveal the fundamental pathways of SARS-CoV-2 replication.

There is also interest in testing whether immunotherapy or biological therapies, such as convalescent plasma and hyperimmune globulin, containing antibodies isolated from blood donated by people who have recovered from COVID19, could shorten the length or reduce the severity of the illness. Furthermore, by studying the protective function of memory immune cells from recovered patients, it may be possible to develop prophylactic and therapeutic approaches to cope with future coronaviruses outbreaks. Treatment of SARS-CoV-2 infection with antibody-based and vaccine-based therapies requires an understanding of how neutralizing antibodies identify and eliminate the virus. The role of humoral immune responses in preventing SARS-CoV-induced lung damage is controversial. In fact, there have been reports of SARS-related mortality in patients who have developed strong neutralizing antibodies. Because these antibodies have been associated with the secretion of proinflammatory cytokines in the lungs, it has been hypothesized that they may be linked to fatal acute inflammatory lung injury. In addition, SARS-CoV-2 may be effectively treated with the administration of MSCs, which are supposed to possess paracrine and immunomodulatory effects on immune cells. It will be necessary to perform randomized clinical trials to assess the effects of MSCs as a potential treatment for COVID19. The immunomodulatory and anti-inflammatory effects of MSCs could be enhanced by pre-exposure to factors such as IFNγ in the presence or absence of TNF-α or IL-1 (i.e., licensing-approach). This is important because T cells are generally

Table 8
Selected cell-based therapies against SARS-CoV-2 in clinical trials.

Phase	Responsible party	Interventions	Recruitment status	Population (enrollment and age)	NCT number
1, 2	Beijing 302 Hospital	● MSCs ● Saline containing 1% human serum albumin (solution of MSCs)	Recruiting	90 18–75	NCT04288102
1	Beijing 302 Military Hospital	● MSCs	Recruiting	20 18–70	NCT04252118
Not applicable	Puren Hospital Affiliated to Wuhan University of Science and Technology	● UC-MSCs	Recruiting	– 18–75	NCT04293692
Early 1	CAR-T (Shanghai) Biotechnology Co., Ltd.	● Dental pulp MSCs	Not yet recruiting	24 18–75	NCT04302519
2	Zhongnan Hospital	Biological: UC-MSCs	Recruiting	10 18–75	NCT04269525
2	Tianhe Stem Cell Biotechnologies Inc.	Combination product: stem cells and mononuclear cells isolated by apheresis	Not yet recruiting	20 18–60	NCT04299152
1	Ruijin Hospital	● MSCs-derived exosomes	Not yet recruiting	30 18–75	NCT04276987
1	Azidus Brasil	● NestCell®	Not yet recruiting	66 ≤18	NCT04315987
Not applicable	Wuhan Union Hospital	● UC-MSCs	Not yet recruiting	48 18–60	NCT04273646
1, 2	Chongqing Public Health Medical Center	● NK cells, IL15-NK cells, NKG2D CAR-NK cells, ACE2 CAR-NK cells and NKG2D-ACE2 CAR-NK cells	Recruiting	90 ≤18	NCT04324996
1	Stem Cells Arabia	● WJ-MSCs	Recruiting	5 ≤18	NCT04313322
1	Xinxiang medical university	● NK cells	Recruiting	30 18–65	NCT04280224

poorly activated in patients with SARS-CoV-2 infection, and therefore stimulating factors, such as interferons, may be low in these patients. The cytokine-licensed MSCs can effectively inhibit hyperactive immune responses and promote tissue repair.

In conclusion, despite many studies in humans, there is not yet an optimal treatment for SARS-CoV-2 infection. Detailed laboratory studies and further clinical trials will be required to establish evidence-based treatment for patients with SARS-CoV-2 as well as ARDS.

CRediT authorship contribution statement

F.O. and A.M. wrote the article. A.H., N.H., B.B., H.B.B., M.A.S, M.R.H., H.A.S. contributed in the correction and editing of the manuscript.

Declaration of competing interest

MRH declares the following potential conflicts of interest. Scientific Advisory Boards: Transdermal Cap Inc., Cleveland, OH; BeWell Global Inc., Wan Chai, Hong Kong; Hologenix Inc. Santa Monica, CA; LumiThera Inc., Poulsbo, WA; Vielight, Toronto, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics LLC, Cambridge, MA; Global Photon Inc., Bee Cave, TX; Medical Coherence, Boston MA; NeuroThera, Newark DE; JOOVV Inc., Minneapolis-St. Paul MN; AIRx Medical, Pleasanton CA; FIR Industries, Inc. Ramsey, NJ; UVLRx Therapeutics, Oldsmar, FL; Ultralux UV Inc., Lansing MI; Illumiheal & Petthera, Shoreline, WA; MB Lasertherapy, Houston, TX; ARRC LED, San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc., Boston, MA. Consulting; Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V. Eindhoven, Netherlands; Johnson & Johnson Inc., Philadelphia, PA; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stockholdings: Global Photon Inc., Bee Cave, TX; Mitonix, Newark, DE.

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