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Coronavirus disease 2019 (COVID-19): Immunological approaches and emerging pharmacologic treatments

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ABSTRACT

The SARS-CoV-2 virus is an etiological agent of pandemic COVID-19, which spreads rapidly worldwide. No proven effective therapies currently exist for this virus, and efforts to develop antiviral strategies for the treatment of COVID-19 are underway. The rapidly increasing understanding of SARS-CoV-2 virology provides a notable number of possible immunological procedures and drug targets. However, gaps remain in our understanding of the pathogenesis of COVID-19. In this review, we describe the latest information in the context of immunological approaches and emerging current antiviral strategies for COVID-19 treatment.

1. Introduction

In December 2019, many severe respiratory diseases accompanied by pneumonia appeared in Wuhan, Hubei province, China, with unknown etiology [1–3]. Sequencing examination on lower respiratory tract specimens showed a novel coronavirus named 2019 novel coronavirus (2019-nCoV) [4–8]. Data from genome sequencing of SARS-CoV-2 assist the researchers in approving diagnostic examination, epidemiologic tracking, and advancement of preventive and curative strategies [9]. The clinical sign of COVID-19 has a wide range from moderate, self-restraint respiratory tract illness to acute progressive pneumonia, multi-organ collapse, and death [9,10]. Up to the present, there were no licensed therapies for the therapy of 2019-nCoV infection. After the rise of the SARS-CoV-1 in 2003, screening of licensed drugs for the therapy of SARS led to the identification of some drugs (as reviewed by Vijayanand and colleagues) [11], such as protease inhibitors, nucleoside analogs, intravenous immunoglobulins, convalescent sera, tumor necrosis factor-alpha blockers, interferons, traditional Chinese medicines, and glycyrrhizin. This virus causes SARS in humans [11]. There are no confirmed efficacious treatments for the COVID-19; however, researchers made much effort to develop antiviral strategies for the treatment of COVID-19. This review will describe the current evidence on significant proposed, repurposed, or experimental therapies for COVID-19 and present a summary of contemporary clinical experience and treatment guidelines for this new pandemic SARS-CoV-2.

2. Immunological approaches

2.1. Human monoclonal antibody

Antibodies are an essential part of host immune reactions to viral infection. Due to their unique maturation process, antibodies can emerge extremely particular to viral antigens [12]. The first use of immunoglobulins (antibodies) as a therapy opportunity for viral diseases can be hunted back to the beginning 20th century, using sera of infected people, who had improved from the same condition [13,14]. This natural therapy regimen (serum therapy), was slowly replaced by immunoglobulins purified from merged sera, intravenous immune globulin (IVIG) [15]. Notwithstanding the achievement of both serum therapeutics and IVIG, no meaningful advancement was made to produce antibodies as therapeutics. The hybridoma technique was

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continuously launched, facilitating the separation of monoclonal antibodies (mAbs) from immunized mice in 1975 [16]. Various approaches have been established since the mid-1980s for the effective separation of mAbs toward viruses of human and animal sources [12]. To date, there are no confirmed vaccines or therapeutic medications that are special to COVID-19. Preventing monoclonal antibodies (mAbs), owing to their fantastic antigen specificity, is among the most suitable nominees for compensating viral infection [17]. Hence, recognizing and cloning of mAbs that can accurately target viral superficies proteins to hinder the viral entrance to host cells is an acceptable strategy for blocking and handling COVID-19, mainly when effective vaccines and therapeutics medications are unavailable in the outbreak of the COVID-19 pandemic [18]. mAbs targeting exposed positions on viral outside proteins are frequently identified as hopeful classes of drugs toward infectious disorders and have conferred therapeutic potency for numerous types of viruses [19,20]. Neutralizing antibodies produced against coronavirus mainly target the spike (S) glycoproteins outside the viral envelope that mediates entrance into host cells.

The S protein is composed of two functional subunits, which involve cell binding (S1 subunit) and S2 subunit, which includes membrane fusion. S1 subunit the main target of the humoral immune system, that Potent neutralizing antibodies often produced against it [21–26]. A recent report by Wang et al. has shown that human mAbs can neutralize both SARS-CoV-2 and SARS-CoV in cell culture [27]. Another report demonstrated that Chen and colleagues separated two human mAbs employing SARS-CoV-2 RBD-specific memory B cells separated from healed cases with COVID-19. These two mAbs could especially attach to SARS-CoV-2 RBD, block the interplay within SARS-CoV-2 RBD and the hACE2 receptor, and lead to potent neutralization of SARS-CoV-2 S protein pseudotyped virus infection. Before-mentioned human anti-SARS-CoV-2 RBD-ACE2 blocking mAbs are initially described and endure transcendent hope to be employed as specific preventive and therapeutic tools toward underway SARS-CoV-2 pandemic [18]. This knowledge suggests that mAbs have a promising approach for tackling the COVID-19 pandemic. The results of using mAbs are still premature, and future studies will shed light on the feasibility of this type of biological therapy for patients with COVID-19 (Fig. 1) (Table 1).

2.2. Convalescent plasma (CP) therapy in severe COVID-19 patients

The sera separated to form recovered patients from the infectious disease called Convalescent plasma, which has been employed to prevent and treat various infectious illnesses for longer than one century. Antibodies exist in immune or convalescent plasma, intercede their curative effects through multiple mechanisms. The antibody can attach to a given infectious agent by compensating its infectivity directly. Another mechanism that antibody may also contribute to its therapeutic effect includes complement activation, phagocytosis, and antibody-dependent cellular cytotoxicity. Non-neutralizing antibodies attach to the infectious agent but do not intervene with their capacity to replicate in-vitro systems may also participate in prevention and expedite the rehabilitation process [28,29]. Across the previous two decades, convalescent plasma therapy has been successfully employed to manage SARS, MERS, and the 2009 H1N1 pandemic with competent potency and safety [30–33]. A meta-analysis of 32 investigations of SARS-CoV and severe influenza virus infection explained a statistically meaningful decline in the pooled odds of fatality following treatment with convalescent plasma, contrasted with placebo or no treatment [34]. However, convalescent plasma treatment was unable to considerably enhance the durability of the Ebola virus infection, presumably due to the lack of data on neutralizing antibody titration for stratified examination [35]. Because the virological and clinical features share similarities between SARS-CoV-1, MERS, and SARS-CoV-2, convalescent plasma treatment might be a confident strategy choice for COVID-19 saving [36]. Patients who have healed from COVID-19 with a huge neutralizing antibody concentration may be a precious donor reservoir of convalescent plasma. It is worth mentioning that there are potential safety concerns on convalescent plasma therapy, including transmitting other infectious agents and a pathological event called antibody-dependent enhancement (ADE) [37]. ADE attributes to a means of how antibodies increasing throughout a previous infection exacerbate clinical severity as an outcome of disease with a distinct viral serotype. This event is famed for some viruses, prominently the Dengue virus [38].

Although, in convalescent serum trials, attention, and alertness to recognize any enhanced infection, evidence will be demanded. In a recent report published in China, researchers revealed that in 10% of patients, one dose of convalescent plasma (200 mL) was well-tolerated and significantly increased or maintained neutralizing antibodies at high levels, resulting in the disappearance of viremia within a week. It can also modulate multiple parameters compared to pre-transfusion, including decreased C-reactive protein and increased lymphocyte numbers. Besides, convalescent plasma therapy in seven cases who had the former viremia led to the disappearance of viremia (undetectable viral load). Another finding that study was that convalescent plasma treatment was well-tolerated and conceivably improved the clinical symptoms, thereby neutralizing viremia in patients with severe COVID-19. Finally, the authors of this study believe that further investigations are wanted to define the optimal dose and clinical benefits of convalescent plasma therapy [39]. Future studies should analyze the efficiency of convalescent plasma treatment in many patients, and the potential risk of this therapeutic method must be deeply assessed (Fig. 1) (Table 1).

2.3. Cytokines-targeted therapy for COVID-19

The increasing knowledge is regarding COVID-19 pathogenesis has supported the role of excess inflammatory mediators in patients with COVID-19. Patients' pathological characteristics with COVID-19 include capillary leakage of liquid and entrance of inflammatory cells, including T cells, neutrophils, and macrophages [40], referring a function for chemokines and cytokines targeting vascular endothelium. The concentration of pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, and IFN-γ, are elevated in the blood of cases infected with COVID-19 [3,41]. Recent studies report different cytokine profiles in patients with severe COVID-19 [3,41–46]. In a study carried out by Huang and colleagues have revealed the higher concentration of IL-2, IL-7, IL-10, TNF, G-CSF, IP-10; CXCL10, MCP-1 (CCL2) and MIP-1A (CCL3), but not IL-6, in cases hospitalized in the intensive care unit (ICU) contrasted with non-ICU patients (4). Another study confirmed that during acute COVID-19 disease, some pro-inflammatory cytokines such as IL-1β, IL-1Ra, IL-2R, IL-6, IL-8 (CXCL8), IL-17, IFN-γ, GM-CSF elevated [42–46]. In recent exciting research, the concentration of some cytokines/chemokines, including IL-6, IL-10, IFN-γ, TNF, and IP-10 in ICU patients with COVID-19, have been higher than mild to moderate non-ICU patients [3,42–44]. Various strategies, including global targeting of the inflammation or compensating a single crucial inflammatory marker, are applied to cope with cytokine storm in COVID-19. Between key cytokines, IL-6 has drawn significant attention levels, and antibodies that hinder the IL-6 receptor (IL-6 antagonist, tocilizumab, and sarilumab) are now following phase 2/3 clinical trials for the possible therapy of COVID-19 [47]. Another hopeful strategy is targeting IFN-γ, which has been remarked by beginning a clinical trial for JAK-STAT inhibitor (ruxolitinib) for managing COVID-19 severity [48]. TNF works upstream of IL-6, and anti-TNF treatments earlier revealed protecting impacts in deadly SARS-CoV disease [49]. A recent report by Cavalli et al. have shown that the efficacy of anakinra (human interleukin-1 receptor antagonist protein) was notably higher in subjects with COVID-19 contrasted with those who received standard treatment for three weeks, led to decreased levels of serum CRP, improved respiratory function (72% vs. 50%), increased survival rate (90% vs. 56%). However, the study results demonstrated that bacteremia's risk

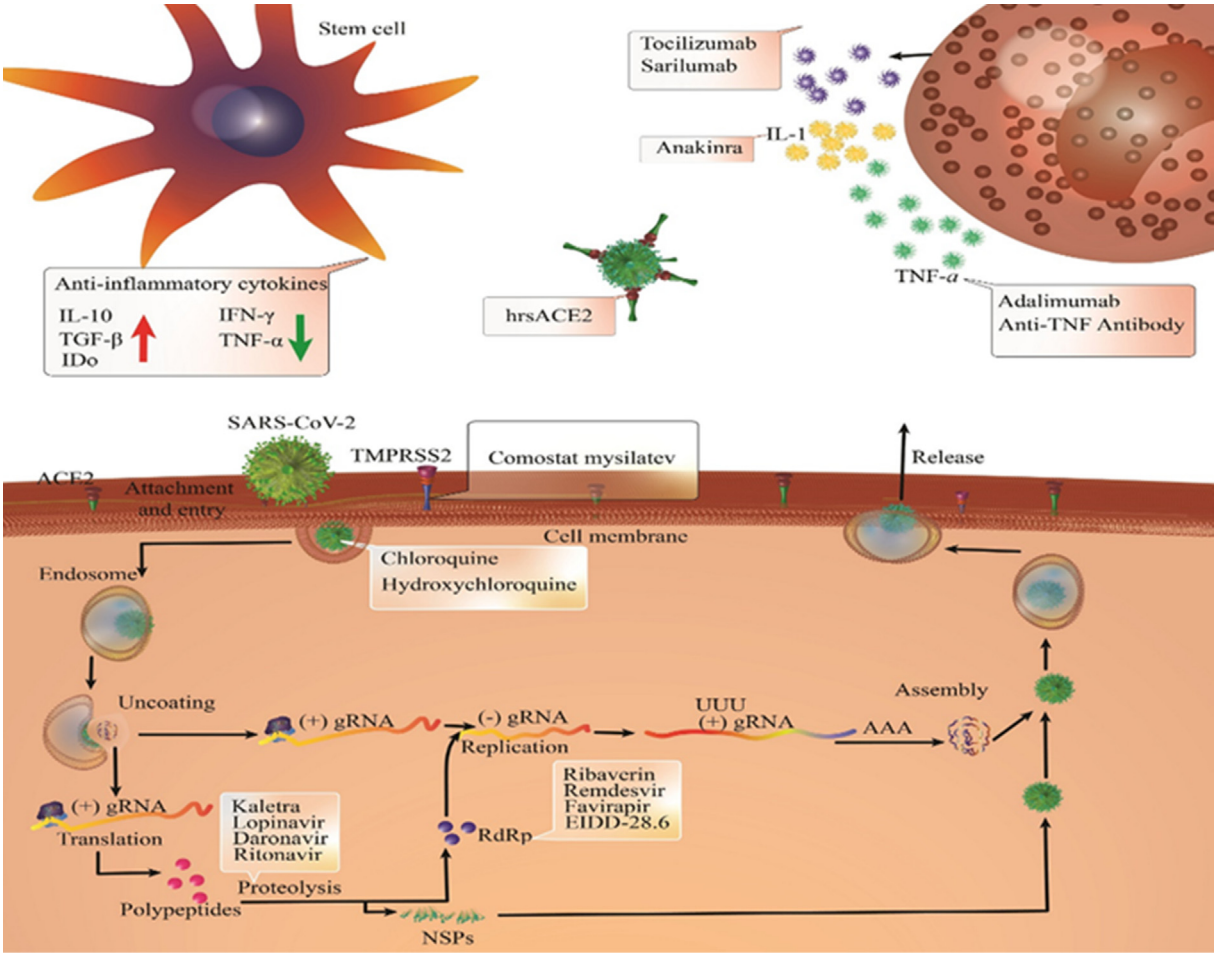

Fig. 1. Schematic represents the action of the mechanisms of candidates' drugs for treatments COVID-19.

was elevated in cases receiving anakinra than those receiving standard treatment [50]. Although there is no particular antiviral medicine for COVID-19, knowledge of cytokine storm mechanisms can help to speculate possible therapeutic interventions (Fig. 1) (Table 1) [51].

2.4. Corticosteroids

It is alleged that corticosteroid treatment is not supported for viral pneumonia [52]. Investigations have revealed that the use of systemic corticosteroids for patients with SARS-CoV and MERS-CoV was correlated with a higher fatality rate than patients under standard treatment [53,54]. The same finding was described in cases with influenza virus-associated pneumonia [55]. In a study performed by Matsuyama et al. [56], they utilized the nasal administration of corticosteroids for patients infected with coronaviruses. They indicated that in the cell culture models, the inhaled form of corticosteroids, such as Ciclesonide, could be useful for the treatment of coronaviruses. Ciclesonide exerts antiviral and anti-inflammatory activity in *in-vitro* models [56].

Furthermore, there are some open clinical trials for the therapeutic assessment of methylprednisolone on COVID-19 patients [57]. A systematic review study carried out by Tahvildari and colleagues [58], shows that at least six different published studies on the effect of corticosteroids on COVID-19 patients. Also, Wu *et al.* [59] indicated that the use of corticosteroids for patients with COVID-19 who developed ARDS could lead to a better outcome and reduce the mortality rate. These results indicate the necessity of checking the clinical conditions of COVID-19 patients before prescribing corticosteroids. Finally, recently, a case report study from Japan shows that orally inhaled ciclesonide alleviates the local inflammation in the lung of patients with COVID-19 pneumonia and inhibits the propagation of the virus by antiviral activity [60]. Further studies are required to unravel the precise mechanism of corticosteroids in the exacerbation of patients with COVID-19 (Fig. 1) (Table 1).

2.5. Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are a subset of non-hematopoietic adult stem cells, readily isolated from various tissues. They show immunoregulatory activity and could be employed for the tissue repair process as they secrete paracrine factors [61]. Cell-based therapy, remarkably stem cell therapeutics, has become an encouraging remedial field, in which many perceive possibilities to cure deadly and inflammatory disorders [62,63]. Notwithstanding the notable progress of stem cell-based treatment, immunogenicity, poor cell source, and moral problems are deemed the main therapeutic approach restrictions. Among these, MSCs have drawn much attention due to origin potential, a high reproduction speed, having a low invasive method, and free of moral problems. There is an extreme advantage in applying MSC treatment in contrast with other approaches [64]. The results indicate that following COVID-19 infection may start suppressing immune overactivity in the human body. In patients infected with SARS-CoV-2, the immune system generates massive volumes of inflammatory factors, prompting cytokine storm in which the immune cells produce an extreme amount of cytokines and chemokines [65]. Herein, it is the opening of the MSC therapy strategy in the treatment of COVID-19 patients. MSC cure can limit the storm release of cytokines by the immune system and raise endogenous restoration by regenerative features of stem cells [66]. Recently, some countries, such as China, the USA,

Table 1
Presentation of immunological approaches and emerging drugs for select suggested COVID-19 treatments.

Drugs	Mechanism of action	In vitro	In vivo and Trials or Clinical Experience note
Hydroxychloroquine (HCQ)	Inhibit the fusion of the virus to the cell membrane by modulation of the endosomal pH	In Vero cells hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 [73,138]	HCQ could significantly shorten TTCR and promote the absorption of pneumonia [139] HCQ significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin [77] HCQ no effect on intubation or death in patients with COVID-19 [80] HCQ did not substantially reduce symptom severity in outpatients with early, mild COVID-19 [82]. HCQ has no benefit in patients with mild Covid-19 [83]. HCQ with or without azithromycin was not significantly associated with differences in in-hospital mortality [140] HCQ alone or with azithromycin in patients with COVID-19 was associated with a decline in COVID-19 associated mortality[84].
Chloroquine phosphate	Inhibit the fusion of the virus to the cell membrane by modulation of the endosomal pH	In vitro activity against SARS-CoV-2 in infected Vero E6 cells reported; some evidence it may block infection in Vero E6 cells exposed to SARS-CoV-2 [75,104,138]	Clinical experience in treating pts with COVID-19 accumulating; reports of possible clinical benefits, including decrease in viral load and duration of illness [53,71,75]
Favipiravir (FPV)	RNA polymerase inhibitor	In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug [104,105,141]	FPV significantly improved the latency to relief for pyrexia and cough [99] FPV in patients with COVID-19 led to decrease of viral load and significant improvement in chest imaging compared with the control arm [98]
Remdesivir	RNA polymerase inhibitor	In Vero E6 cells remdesivir inhibits SARS-CoV-2 replication [104,105]	Remdesivir was not associated with statistically significant clinical benefits [107] Clinical improvement was observed in 68% of severe Covid-19 patients treated with remdesivir in a cohort study [142] Remdesivir was associated with shortened recovery time and decreased rate of mortality in patients with COVID-19 versus the placebo group [109]
EIDD-2801	RNA polymerase inhibitor	EIDD-2801 inhibits SARS-CoV-2 in human airway epithelial cell cultures [143]	
ACE Inhibitors	ACE inhibitors or ARBs may effect in terms of virus binding		Clinical trial underway: Initiation of losartan in adult patients with COVID-19 requiring hospitalization; primary outcome measure: sequential organ failure assessment (SOFA) respiratory score (NCT04312009)
hrsACE2	Inhibition of viral entry into the cell	In vitro hrsACE2 had a dose dependent effect of viral growth of SARS-CoV-2 and was able to reduce it by a factor of 1,000 to 5,000 in cell cultures [89]	Currently no known published data regarding efficacy or safety in the treatment of COVID-19
Ivermectin	Inhibiting IMPα/β1 which mediated nuclear import of viral proteins in some human and animal viruses.	In vitro activity against some human and animal viruses In vitro evidence of activity against SARS-CoV-2 in infected Vero-hSLAM cells reported with high concentrations of the drug [118]	Currently no known published data regarding efficacy or safety in the treatment of COVID-19
Convalescent plasma	Bind to SARS-CoV-2 and neutralized its infectivity, complement activation, phagocytosis, and antibody-dependent cellular cytotoxicity		In patients with SARS-CoV-2 infection, the use of convalescent plasma was reported to increase neutralizing antibody, decreased viral load, and CRP, improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases [39] The recent retrospective study in 6 severs COVID-19 patients were treated with convalescent plasma at a median of 21.5 days after the first detection of viral shedding. Although viral clearance was observed in all patients following transfusion, death occurred in 5 out of 6 patients [144] In a descriptive study in china various laboratory, radiologic, and clinical improvements were improved in patients with COVID-19 that received convalescent plasma [145] Some of the trials that are currently recruiting are listed below: NCT04374370 NCT04358211

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Table 1 (*continued*)

Drugs	Mechanism of action	In vitro	In vivo and Trials or Clinical Experience note
			NCT04338360 NCT04363034 NCT04343261 NCT04372368 NCT04343755 NCT04344535 NCT04364737 NCT04340050 NCT04344015 NCT04376034 NCT04359810 NCT04362176 NCT04360486 NCT04347681 NCT04346446 NCT04345523 NCT04342182 NCT04352751 NCT04375098 NCT04357106 NCT04327349 NCT04292340
Anakinra	Recombinant human interleukin-1 (IL-1) receptor antagonist, may potentially combat cytokine release syndrome (CRS) symptoms in severely ill patients		In patients with COVID-19, anakinra decreased serum CRP, improvements in respiratory function, and also the survival rate increased about 90% [50]
Ruxolitinib	Janus kinase (JAK) 1 and 2 inhibitor		Phase 3 randomized, double-blind, placebo-controlled clinical trial (NCT04362137; RUXCOVID) evaluating ruxolitinib plus standard of care vs standard of care alone is being initiated in patients ≥ 12 years of age with COVID-19-associated cytokine storm [9,146–148] Some clinical trial registered at clinicaltrials.gov: NCT04331665 NCT04334044 NCT04338958 NCT04348071 NCT04359290 NCT04354714 NCT04348695
Tocilizumab	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor		Case reports and observational investigations describe the effectiveness of tocilizumab in patients with COVID-19 described from various areas of the world. Currently, there are no well-controlled published researches on the effectiveness and safety of tocilizumab for the treatment of COVID-19; however, various clinical trials are designed or underway globally [9,149]
Siltuximab	Recombinant chimeric monoclonal antibody specific for the interleukin-6 (IL-6) receptor		Primary (non-peer-reviewed) judgments from an observational case-control investigation of the initial 21 patients withCOVID-19 and ARDS who engaged in a compassionate treatment program (SISCO study; NCT04322188) in one hospital and were tracked for up to 7 days displayed diminished and normalized C-reactive protein (CRP) levels at day 5 in all 16 Siltuximab-treated patients with adequate, accessible data. An interim examination revealed that 33% of the Siltuximab-treated patients recovered, and no clinically related change in condition was described in 43% of patients. In comparison, 24% of patients worsened, including one patient who died and another with a cerebrovascular occasion. This cohort investigation with patients treated with standard therapy is continuing [150] Other clinical trial registered: NCT04329650 NCT04330638
Corticosteroids	Potent anti-inflammatory and antifibrotic properties; use of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia		Uncontrolled observational data of the novel COVID-19 outbreak in China propose a reasonable treatment profit of methylprednisolone in COVID-19 patients with acute respiratory distress syndrome [59,151].

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Table 1 (*continued*)

Drugs	Mechanism of action	In vitro	In vivo and Trials or Clinical Experience note
			Orally inhaled ciclesonide used in the case series from Japan in COVID-19 patients with pneumonia was associated with mitigating the local inflammation and inhibit the proliferation of the virus [60]. Other clinical trials have been launched in numerous countries to judge the use of IV corticosteroids: NCT04327401 NCT04344288 NCT04344730 NCT04348305 NCT04355637 NCT04359511 NCT04360876
Baricitinib	Janus kinase (JAK) 1 and 2 inhibitor		Currently, no known published controlled clinical trial evidence confirming efficacy or safety in patients with COVID-19 In a small (12 patients) open-label study in Italy (NCT04358614), use of baricitinib in combination with lopinavir/ritonavir was assessed in patients with mild COVID-19 pneumonia [152] Some clinical trial registered at clinicaltrials.gov: NCT04340232 NCT04340232 NCT04321993 NCT04346147 NCT04320277 NCT04321993
Nonsteroidal Anti-inflammatory Agents (NSAIAs)	Ibuprofen: Speculative link between ibuprofen and increased ACE2 expression leading to worse outcomes in COVID-19 patients, and should not be used in patients with COVID-19 [153] Indomethacin: Possible antiviral activity against other coronaviruses SARSCoV (interferes with viral RNA synthesis) [154]	In vitro activity against SARS-CoV [154]	
Anticoagulants	Modulate coagulation abnormalities		A randomized open-label clinical trial (NCT04345848) is currently being conducted to evaluate prophylactic- and therapeutic-dose anticoagulation in hospitalized adults with severe COVID-19 infection
Neuraminidase inhibitors	Antivirals active against influenza viruses	In vitro investigations indicated oseltamivir and zanamivir has inhibitory effects against SARS-CoV in cell culture [155]	While oseltamivir is regarded to have been broadly used for confirmed or suspect COVID-19 states in hospitals in China, there has been no conclusive confirmation to date that oseltamivir is beneficial in the treatment of COVID-19 [156] Clinicaltrials.gov trials for COVID-19 that involve oseltamivir: NCT04303299 NCT04261270 NCT04255017 NCT04338698
HIV Protease Inhibitors	Inhibits 3–chymotrypsin like protease	Lopinavir (LPV) has in vitro activity against SARS-CoV-2 in Vero E6 cells [157] Atazanavir (ATV) alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells [157,158] Nelfinavir, Saquinavir, and Tipranavir have n vitro activity against SARS-CoV-2 in Vero E6 cells [157]	LPV and RTV randomized, open-label trial in China in hospitalized adult patients with severe COVID-19 infection compared LPV/RTV in combination with standard care remark that LPV–RTV treatment has no benefit beyond standard care [159] A retrospective cohort study in China evaluated the use of LPV/RTV with or without umifenovir in adults. The results of this study indicated that the apparent favorable clinical response with arbidol and LPV/RTV supports further LPV/RTV only [160] LPV/RTV COVID-19 Clinical Trials at clinicaltrials.gov: NCT04307693 NCT04276688 NCT04328012 Darunavir COVID-19 Clinical Trials: NCT04252274 NTC04303299 ChiCTR2000029541

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Table 1 (*continued*)

Drugs	Mechanism of action	In vitro	In vivo and Trials or Clinical Experience note
			A retrospective investigation in China suggests that patients with severe COVID-19 infection or notably elevated levels of D-dimer may have diminished mortality if given prophylactically; however, the current study has limited data [137] A randomized open-label clinical trial is currently being administered to assess preventive and therapeutic dose anticoagulation agents in hospitalized adult patients with severe COVID-19 infection: NCT04345848

Iran, and various other countries, have launched MSC therapy, and some reports are currently available in the published literature. MSCs, working their immunomodulatory features and their differentiation capacity, can inhibit lung tissue loss by hindering the cytokine storm and restoration and regeneration of damaged tissues [67]. A recent study carried by Chen and co-workers indicated that the use of MSCs notably improves the survival proportion of H7N9-induced ARDS and provides a philosophical background for treating H7N9-induced ARDS preclinical research and clinical research. Because H7N9 and COVID-19 share similar complications and are associated with multi-organ collapse, MSC-based treatment could be a feasible option for the treatment of COVID-19 [68]. In the same way, a recent case-report study showed that the adoptive transfer therapy of human umbilical cord blood derived-mesenchymal stem cells (hUCMSCs) to a Chinese female patient afflicted with acute COVID19 syndromes improved her laboratory tests and CT images [69]. Before receiving any treatments, the percentage of her neutrophils was increased to 87.9% while the number of lymphocytes was decreased to 9.8%. She was operated with antiviral medications, including lopinavir/ritonavir, IFN-α, and oseltamivir, also the intravenous dose of moxifloxacin, xuebijing, methylprednisolone, and immunoglobulins. The case was also curbed to non-invasive mechanical ventilation to expedite breathing and decrease muscle weakness due to weak oxygenation. As the vital symptoms exacerbate, the case was treated with hUCMSCs solely and with α1 thymosin 5 × 107 cells per three times. The study results explained that following the second injection, serum albumin, CRP, ALT, and AST were steadily diminished, and other important symptoms were enhanced. After that, the patient was discharged from the ventilator and capable of walking, and the number of neutrophils and white blood cells returned to the baseline levels. Most importantly, the abundance of CD3+, CD4+, and CD8 + T cells was significantly enhanced. Also, the qualitative outcomes of CT images following the second and third doses of hUCMSCs revealed that pneumonia was attenuated. After two days of the third injection, the patient was rescued from the ICU, and most of the vital symptoms and clinical laboratory parameters returned to the standard ranges. The outcomes recommended that hUCMSCs could be an excellent strategy choice alone or in combination with other immunomodulatory tools for COVID-19 patients [69]. A recent study performed in China in cooperation with the United States recruited seven cases with COVID19 pneumonia from January 23 to February 16. Patients experienced MSCs transplantation, and their clinical signs were consecutively checked for 14 days. The study demonstrated that the transplantation of hUCMSCs led to a marked decrease in the level of pro-inflammatory cytokines and a substantial improvement in clinical symptoms without any significant adverse effects [70]. The pulmonary function, along with the seven patients' clinical symptoms, were significantly improved after two days of transplantation. The number of peripheral lymphocytes also increased, while CRP concentration was diminished after the treatment. Additionally, the number of hyperactive cytokine-secreting immune cells, namely CXCR3 + CD4+, CXCR3 + CD8+, and CXCR3 + NK cells was remarkably lowered within 3–6 days after transplantation of hUCMSCs. Moreover, the frequency of CD14 + CD11c + CD11b mid regulatory DC cell population was significantly elevated. The level of TNF-α was significantly reduced, while IL-10 was raised in the hUCMSCs-treated group contrasted with the placebo control group. Besides, the gene expression characterization explained that ACE2 and TMPRSS2 genes are not expressed in hUCMSCs, implying that the coronavirus would not infect these cells. Hence, the intravenous transplantation of hUCMSCs is seemingly safe and efficient for the treatment of cases with COVID-19 pneumonia, notably those in critically severe conditions [70].

As multiple clinical trials are launched worldwide, we should not have to wait long to determine if MSCs are a viable and valid treatment choice for severe COVID-19. Considering the need for mitigating the prevailing COVID-19 pandemic, with superiority to manage fatality as low as possible, the judgment that MSC is reliable and can invert severe critical disease with high power is an invention designing a completely novel biological procedure that needs to be developed urgently(Fig. 1) (Table 1).

3. Other pharmacologic therapies

3.1. Chloroquine and hydroxychloroquine (HCQ)

Chloroquine and HCQ are both known as antimalarial drugs. Clinical studies introduced these two drugs as a possible choice for COVID-19 treatment due to having in-vitro antiviral and anti-inflammatory properties [71–74]. Several studies suggested that chloroquine could improve the radiological and virological features of COVID-19 [53]. Chloroquine is a reliable and effective drug for COVID-19 in some preclinical trials [75] and other studies [72]. In this regard, Smith et al. [72] indicated that cardiac arrhythmia is a significant side effect of chloroquine. In the matter of hydroxychloroquine, reports are controversial [72,73,76]. In a study conducted by Shamshirian et al. [76], there was no potential clinical efficacy in prescribing HCQ. Simultaneously, the in-vitro anti-SARS-CoV-2 activity of this particular drug seems to be more than chloroquine [72,73]. Fortunately, there are currently several clinical trials being conducted on these drugs [57]. Also, regardless of the solo practice for these drugs, Gautret, and colleagues [77] suggested a combination of HCQ and azithromycin as an effective treatment for decreasing the viral load in patients with COVID-19. Another aspect of these drugs is the possibility of using them in different conditions such as pregnancy. A majority of studies conducted on HCQ did not reflect any serious concerns, and this drug seems to be safe for pregnant women [78]. Besides, as mentioned by Lother et al. [79], clinical trials for the assessment of medicines as post-exposure prophylaxis could be helpful.

A recent report noted that the severity of COVID in patients treated with HCQ was higher than those not receiving this medication. Also, the report showed that there was no meaningful correlation within the use of HCQ and intubation or mortality [80]. Besides, another report demonstrated that amongst cases hospitalized in metropolitan New

York with COVID-19, practice with HCQ, azithromycin, or both, matched with neither medication, was not meaningfully correlated with variations in an in-hospital fatality. However, the analysis of these conclusions may be restricted by the observational study [81]. The recent study also indicated that HCQ did not substantially decrease symptom severity in outpatients with early, mild COVID-19 [82]. At the same time, another study performed by Mitjà and colleagues indicated that HCQ in patients with mild COVID-19 has no benefit beyond routine care [83]. Moreover, Arshad and co-workers [84] showed that in patients with COVID-19 treated with HCQ alone and combined with azithromycin, it was correlated with a decline in COVID-19 associated mortality. Comprehensive systematic review and meta-analysis studies and clinical trials in this field are urgently needed (Fig. 1) (Table 1).

3.2. ACE inhibitors and hrsACE2

ACE2 (angiotensin-converting enzyme-2) is a transmembrane enzyme expressed on the exterior of epithelial cells in the many organs such as lungs, arteries, heart, kidney, and intestines [85,86]. Recently, the new coronavirus is responsible for pandemic COVID-19, SARS-CoV-2 is thought to be mainly or exclusively bound to ACE2 [87,88]. The molecular interplay among ACE2 and spike has been created [87,88], and manufactured compounds or antibodies, interfering with the interplay of ACE2, and the viral spike protein could be produced. Another therapeutic approach is the use of soluble ACE2 as a virus scavenger and neutralizer. Soluble ACE2 formed by a proteolytic splitting of the membrane anchor is ordinarily located in the plasma; however, its concentration is shallow. An increase in the availability of soluble ACE2 at tissue positions would change the rivalry with membrane-bound ACE2 toward the soluble form, leading to the repression of viral entry into the cells. It is also expected that this approach would preserve tissue ACE2 [89,90]. A new study has recently shown that the recombinant form of ACE2 reduces the infection and viral growth in cell culture and organoids by acting as a decoy for SARS-CoV-2 [89]. This study showed that by adding a genetically altered variant of ACE2, termed human recombinant soluble angiotensin-converting enzyme 2 (hrsACE2), the entry of COVID-19 into the lung epithelial cells was halted. In this study, the results of cell culture indicated that hrsACE2 decreased the load of SARS-CoV-2 by 1000–5000 times [89]. The authors also used the blood vessels and kidney organoids to explain that SARS-CoV-2 could directly contaminate and propagate in these tissues, suggesting a potential agent of multi-organ collapse and cardiovascular damages as a result of COVID-19. The augmentation of hrsACE2, too, diminished the infectivity of SARS-CoV-2 in these organoids [89]. In engineered models of the human blood artery and kidney organoids developed from human stem cells, it was confirmed that it could straight contaminate and replicate itself in these tissues. These findings provide crucial information about the pathogenesis of COVID-19 and explain the reason for multi-organ collapse and cardiovascular injuries. In this engineered human tissues, hrsACE2 also diminished the viral load of SARS-CoV-2. The researchers highlighted that their experiment has only tested the drug efficacy through the initial stages of SARS-CoV-2 infection. Further investigation would be demanded to determine the fidelity of this recombinant therapy for later stages of the disease (Fig. 1) (Table 1).

3.3. Ribavirin

The prescription of ribavirin for the therapy of coronaviruses returns to SARS-CoV and MERS-CoV. Reports indicated that this antiviral agent's administration did not show promising results for the treatment of SARS-CoV [91]. Meanwhile, ribavirin antiviral activity was addressed in in-vitro studies in a dose-dependent manner [91,92]. On the other hand, a group of studies demonstrated a beneficial role of ribavirin in the treatment of MERS-CoV [93]. Simultaneously, some investigations showed that the combination of ribavirin and interferon was unsuccessful in treating MERS-CoV [94]. There is limited knowledge about the efficiency of ribavirin in the amelioration of COVID-19 [58]. A study conducted by Elfiky *et al.* [95], using bioinformatics approaches, indicated that ribavirin is capable of halting the viral spread of SARS-CoV. Also, based on a study performed by Khalili et al. [96], there are six clinical trials currently assessing the therapeutic effects of ribavirin on COVID-19. Three clinical trials are presently being conducted in China, while the other three clinical trials focused on the combinatory role of ribavirin and other medicines, such as interferons and lopinavir/ritonavir (Fig. 1) (Table 1) [96].

3.4. Favipiravir

Favipiravir (also known as T-705) is an antiviral drug that selectively and robustly hinders the RNA-dependent RNA polymerase (RdRp) of RNA viruses, was licensed in 2014 in Japan to cure pandemic influenza virus diseases [97]. Interestingly, despite its anti-influenza virus activity, this molecule can also halt the replication of an extensive range of RNA viruses (e.g., flaviviruses, alphaviruses, filoviruses, noroviruses, arenaviruses, bunyaviruses, and other RNA viruses) [97]. Regarding the emergence of SARS-CoV-2, it is urgently essential to recognize active antiviral agents to fight the infection and investigate the clinical effects of antiviral drugs. Recently, a clinical trial conducted by Cai et al. highlighted the efficiency of favipiravir in patients with COVID-19 [98]. They indicated that patients receiving favipiravir showed improved chest imaging, faster decreased viral load, and fewer adverse effects than the control group [98]. Another study performed by Chen et al. compared the efficacy of favipiravir versus arbidol [99]. They showed that the clinical recovery rate on day seven and the degree of auxiliary oxygen treatment or non-invasive mechanical ventilation did not significantly vary within the favipiravir- and arbidol-treated groups. Besides, the current study demonstrated that favipiravir significantly enhanced the latency to relief for fevers. Also, adverse effects caused by favipiravir were mild and manageable [99]. These preliminary clinical results provide useful information about therapeutic options for SARS-CoV-2 infection (Fig. 1) (Table 1).

3.5. Remdesivir

Remdesivir (GS-5734) is a prodrug (nucleotide) with extensive antiviral action toward viruses from distinct genera in-vitro [100]. It also has therapeutic effects on nonhuman primate models of deadly Ebola and Nipah virus contaminations [101,102]. Investigations conducted on epithelial cells from human airway explained that remdesivir additionally hinders replicating an extensive range of coronaviruses, including MERS-CoV [103]. Moreover, some reports indicated that remdesivir has robust action toward SARS-CoV-2 in-vitro [104,105].

A recent investigation performed on Rhesus macaques contaminated with SARS-CoV-2 noted that the treatment with a 6-day regimen of IV remdesivir launched 12 h following virus inoculation was correlated with some therapeutic outcomes (lower disease severity rates, less pulmonary infiltrates, lower virus titers in bronchoalveolar lavage samples) contrasted with the control animals. Of note, remdesivir medication did not diminish the viral load or the titer of the virus in the nasopharynx or rectal swabs compared to the control of vehicle control [106]. Various clinical trials are currently being performed in the US, China, and other countries. A recent clinical trial in hospitalized patients with severe COVID-19 in China showed that remdesivir treatment was not correlated with a decline in hospitalized patients' recovery period. The results indicated that patients receiving remdesivir had a lower period of hospital stay than those receiving placebo (18 vs. 23 days); however, such a reduction in hospital stay period was not statistically significant. Also, the continuation of invasive mechanical ventilation was more concise (but not statistically meaningful) in the remdesivir-treated group, and only a tiny percentage of patients (0.4%) underwent invasive mechanical ventilation at the

time of reception. Remdesivir did not significantly reduce the viral load of SARS-CoV-2 in nasopharyngeal, oropharyngeal, and sputum specimens. Remdesivir was stopped in 18 patients (12%) because of adverse effects [107]. However, a phase III randomized, open-label trial performed on hospitalized patients with severe COVID-19 showed that the disease severity was lower in patients who received remdesivir within 10 days after the onset of clinical symptoms compared with those treated after 10 days of the manifestation of clinical signs [108]. Notably, patients treated with remdesivir had a more short recovery period than those treated with placebo. Also, the mortality rate in remdesivir-treated patients (7.1%) was lower than patients receiving a placebo. However, the difference in mortality rate within the two groups was not statistically meaningful [109]. Another clinical trial has been recently established in the US, China, and other countries to explore the efficacy of remdesivir in improving patients with COVID-19 (Table 1). Further clinical trials are wanted to determine the effect of remdesivir on patients with COVID-19 (Fig. 1) (Table 1).

3.6. Ivermectin

Ivermectin is an FDA-licensed drug that has a broad spectrum of antiparasitic activity [110]. Studies have shown that this drug exerts antiviral action toward an extensive range of viruses in-vitro [111–114]. It has been designated that ivermectin hinders the interplay within the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and importin (IMP) α/β1 heterodimer accountable for the nuclear import of IN [115]. Ivermectin has, too, been demonstrated to impede nuclear import and HIV-1 replication [114]. Also, ivermectin suppresses explicitly the activity of the NS3 helicase enzyme, required for the replication of flaviviruses [116].

In the same way, ivermectin inhibits the replication of dengue virus type 2 (DENV-2) in Aedes albopictus [117]. Another study indicated that ivermectin prevents the interaction between DENV 1 and 2 NS5 with its nuclear transporter importin α/β in-vitro and make effort protection toward DENV1-4 [113]. Ivermectin is thought to be effective against SARS-CoV-2, the virus which causes pandemic COVID-19 [118]. It has been reported that ivermectin can reduce the replication of SARS-CoV-2 when added to the cell culture 2 h post-infection. Besides, ivermectin can diminish the viral load by ~5000 folds, whiting 48 h post-infection [118]. The next critical step is to examine dosing regimens that mimic the currently recommended use of ivermectin in humans [119]. A current phase III clinical trial in Thailand showed that ivermectin was safe but did not perform any clinical advantage when used for dengue viruses. However, studies recommended that dosing regimens might be improved and expanded, depending on pharmacokinetic analyses [120]. Although DENV differs from SARS-CoV-2, the design of future clinical trials should be revisited to provide valuable information about the efficacy of this drug on COVID-19. Current studies hold great promise for the prescription of ivermectin as a possible antiviral therapy against SARS-CoV-2 (Fig. 1) (Table 1).

3.7. Eidd-2801

β-D-N4-hydroxycytidine is a ribonucleoside analog called EIDD-1931, an orally bioavailable prodrug by wide range antiviral action toward multiple independent RNA viruses, which includes influenza, Ebola, coronaviruses, and VEEV [121–124]. Currently, there are no specific licensed therapeutics for SARS-CoV-2. Recently, an interesting study indicated the efficacy of EIDD-2801against COVID-19 in human cells and mice [123]. EIDD-2801 is an orally bioavailable drug that its mechanism of action is similar to remdesivir. These drugs can mimic the function of ribonucleosides, the fundamental elements of RNA molecules, making devastating failures when the drugs are combined into viral RNA throughout replication, halting the spread of the virus. However, investigators recommend EIDD-2801 may have some benefits. According to the results of Urakova et al., when EIDD-2801 is used as a prophylactic agent, it would be capable of preventing severe lung injury in infected mice. Besides, in therapeutic administration, it can reduce the viral load and body weight loss if prescribed within 12 and 48 h of infection. This study highlights the potential efficacy of EIDD-2801 for the treatment of SARS-CoV-2 and severe infections caused by other types of coronaviruses [123]. Clinical trials seem to be needed to investigate the probable applicability of EIDD-2801 in the clinic against pandemic COVID-19 (Fig. 1) (Table 1).

3.8. Lopinavir/Ritonavir

Lopinavir and ritonavir are the HIV-1 FDA approved drugs, which inhibitors of the HIV protease. This anti-protease activity seems to be active on the SARS-CoV-2 protease, either. Lopinavir and ritonavir could induce adverse effects, such as QT prolongation, and must be carefully prescribed for patients with liver-associated diseases [72]. Several clinical trials conducted on the combinatory use of lopinavir/ritonavir was more pronounced in patients with COVID-19 than other therapeutic regimens [57,58]. One study also showed that the combination of lopinavir/ritonavir and arbidol (an antiviral agent against RNA viruses) did not significantly protect COVID-19 in patients [125].

Meanwhile, Zhu and colleagues [126] demonstrated that arbidol monotherapy was more effective than the use of lopinavir/ritonavir and arbidol. Besides, an in-vitro study performed on lopinavir did not exhibit any direct antiviral activity against SARS-CoV-2 [74]. Regardless of these findings, the administration of lopinavir/ritonavir seems beneficial on SARS-CoV and MERS-CoV only when used at the early stage of infection [127]. In conclusion, it seems hard to introduce the lopinavir/ritonavir as a treatment option for COVID-19, but further clinical trials are warranted to elucidate the effectiveness of these drugs (Fig. 1) (Table 1).

3.9. Anticoagulation for COVID-19

There is progressing proof that cases with severe COVID-19 promote a hypercoagulable status, which has been correlated with weak outcomes such as increased respiratory malfunction, severe respiratory distress syndrome, or mortality [128–134]. The initial treatment with anticoagulation drugs in patients with severe COVID-19 infection may diminish the risk of thrombotic complexities and promote clinical consequences [59,129,131,133,135].

This increasing evidence urged researchers to focus on the potential applicability of using anticoagulating agents for COVID-19. Heparin is an anticoagulant agent possessing potential benefits beyond anticoagulant activity. It has been shown that heparin decreases coronary thrombosis, pulmonary emboli, and microvascular ischemia. Besides, it has anti-inflammatory and antiviral properties, enabling this compound to lower the degree of lung inflammation and improving oxygenation [136]. A new retrospective report by Tang et al. confirmed that anticoagulant therapy is correlated with a diminished mortality percentage in COVID-19 patients with coagulopathy. Also, the results recommend that patients with severe COVID-19 disease or considerably elevated levels of D-dimer ($> 6 \times$ ULN) may have declined fatality when they receive preventive doses of heparin. Researchers also proposed that anticoagulant treatment seems to be correlated with a more favorable prediction in severe COVID-19 patients engaging sepsis-induced coagulopathy (SIC) standards extended D-dimer [137]. However, prospective studies are demanded to validate these conclusions because the current retrospective study has limited data (Fig. 1) (Table 1).

4. Conclusion

COVID-19 pandemic is an unexpected infectious disease with extensive mortality and morbidity rates that humanity has experienced in the 21st century after the pandemic influenza outbreak of 1918. Although the gaps remain in our understanding of the pathogenesis

COVID-19, the velocity and mass of antiviral strategies began to examine possible medicines for COVID-19 to highlight both the demand and capacity to provide high-quality data even amid a pandemic. Probably the best plan for fighting with the SARS-CoV-2 is an effective vaccine, which prompts the immune system to produce antibodies against viral proteins or T cells that can eliminate infected cells. However, vaccine development is slower than the spread of the epidemic; therefore, the clinically useful candidate drugs would be necessary and urgent for the treatment of patients with COVID-19. Among the immunological approaches, CP therapy might be a trusting approach choice for COVID-19 saving; however, future investigations should examine the efficacy of CP treatment in many patients, and the potential risk of this therapeutic approach must be profoundly evaluated. Besides, many clinical trials are underway across the world; however, currently, no therapies have been shown useful to date for COVID-19, or some drugs such as remdesivir have a limited benefit in patients with COVID19.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106885.

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