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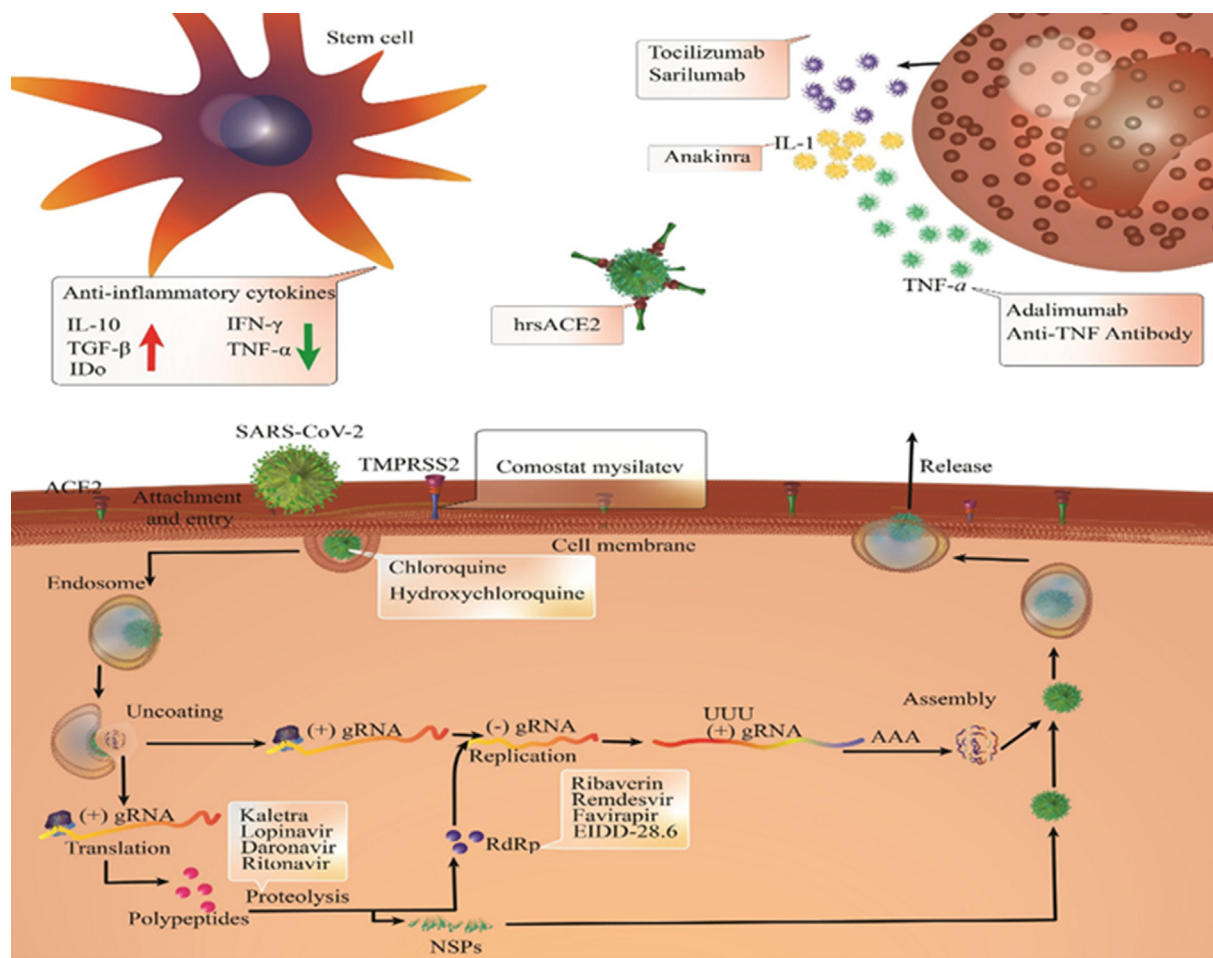
Fig. 1. Schematic represents the action of the mechanisms of candidates' drugs for treatments COVID-19.

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

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].

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) $\alpha/\beta 1$ 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.

Acknowledgments

Appendix A. Supplementary material

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

References

[1] H. Lu, C.W. Stratton, Y.W. Tang, Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle, J. Med. Virol. (2020).
[2] D. Hui, I.E. Azhar, T.A. Madani, et al., The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-the latest 2019 novel coronavirus outbreak in Wuhan, China, Int. J. Infect. Dis. 91 (26) (2020) 4–6.
[3] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, The lancet 395 (10223) (2020) 497–506.
[4] R. Lu, P. Niu, L. Zhao, H. Wang, W. Wang, W. Tan, Sequencing the complete genome of COVID-19 virus from clinical samples using the Sanger Method, China, CDC Weekly 2 (2020) 1–6.
[5] J.-M. Kim, Y.-S. Chung, H.J. Jo, N.-J. Lee, M.S. Kim, S.H. Woo, S. Park, J.W. Kim, H.M. Kim, M.-G. Han, Identification of coronavirus isolated from a patient in Korea with COVID-19, Osong Public Health Res. Perspect. 11 (1) (2020) 3.
[6] W.H. Organization, Novel Coronavirus (2019-nCoV): situation report, 3, 2020.
[7] H. Nishiura, S.-M. Jung, N.M. Linton, R. Kinoshita, Y. Yang, K. Hayashi, T. Kobayashi, B. Yuan, A.R. Akhmetzhanov, The extent of transmission of novel coronavirus in Wuhan, China, 2020, Multidisciplinary Digital Publishing Institute, 2020.
[8] B. Haynes, N.E. Messonnier, M.S. Cetron, First travel-related case of 2019 novel coronavirus detected in United States: press release, Tuesday, January 21, 2020.
[9] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, Jama 323 (18) (2020) 1824–1836.
[10] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, The Lancet 395 (10223) (2020) 507–513.
[11] P. Vijayanand, M.W. Wilkins, Severe acute respiratory syndrome (SARS): a review, Clin. Med. 4 (2) (2004) 152.
[12] G. Salazar, N. Zhang, T.-M. Fu, Z. An, Antibody therapies for the prevention and treatment of viral infections, npj Vacc. 2 (1) (2017) 1–12.
[13] P. Ehrlich, Partial cell functions, Nobel Lecture 11 (1908).
[14] F. Winau, O. Westphal, R. Winau, Paul Ehrlich—in search of the magic bullet, Microbes Infect. 6 (8) (2004) 786–789.
[15] M. Stangel, R. Pul, Basic principles of intravenous immunoglobulin (IVIg) treatment, J. Neurol. 253 (5) (2006) v18–v24.
[16] G. Köhler, C. Milstein, Continuous cultures of fused cells secreting antibody of predefined specificity, Nature 256 (5517) (1975) 495–497.
[17] H.D. Marston, C.I. Paules, A.S. Fauci, Monoclonal antibodies for emerging infectious diseases—borrowing from history, N. Engl. J. Med. 378 (16) (2018) 1469–1472.
[18] X. Chen, R. Li, Z. Pan, C. Qian, Y. Yang, R. You, J. Zhao, P. Liu, L. Gao, Z. Li, Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor, Cell. Mol. Immunol. (2020) 1–3.
[19] P. Prabakaran, Z. Zhu, X. Xiao, A. Biragyn, A.S. Dimitrov, C.C. Broder, D.S. Dimitrov, Potent human monoclonal antibodies against SARS CoV, Nipah and Hendra viruses, Expert Opin. Biol. Therapy 9 (3) (2009) 355–368.
[20] E.O. Saphire, S.L. Schendel, B.M. Gunn, J.C. Milligan, G. Alter, Antibody-mediated protection against Ebola virus, Nat. Immunol. 19 (11) (2018) 1169–1178.
[21] J. Reguera, C. Santiago, G. Mudgal, D. Ordono, L. Enjuanes, J.M. Casasnovas, Structural bases of coronavirus attachment to host aminopeptidase N and its inhibition by neutralizing antibodies, PLoS Pathog. 8 (8) (2012).
[22] X. Yu, S. Zhang, L. Jiang, Y. Cui, D. Li, D. Wang, N. Wang, L. Fu, X. Shi, Z. Li, Structural basis for the neutralization of MERS-CoV by a human monoclonal antibody MERS-27, Sci. Rep. 5 (2015) 13133.
[23] P. Prabakaran, J. Gan, Y. Feng, Z. Zhu, V. Choudhry, X. Xiao, X. Ji, D.S. Dimitrov, Structure of severe acute respiratory syndrome coronavirus receptor-binding domain complexed with neutralizing antibody, J. Biol. Chem. 281 (23) (2006) 15829–15836.
[24] W.C. Hwang, Y. Lin, E. Santelli, J. Sui, L. Jaroszewski, B. Stec, M. Farzan, W.A. Marasco, R.C. Liddington, Structural basis of neutralization by a human anti-severe acute respiratory syndrome spike protein antibody, 80R, J. Biol. Chem. 281 (45) (2006) 34610–34616.
[25] B. Rockx, D. Corti, E. Donaldson, T. Sheahan, K. Stadler, A. Lanzavecchia, R. Baric, Structural basis for potent cross-neutralizing human monoclonal antibody protection against lethal human and zoonotic severe acute respiratory syndrome coronavirus challenge, J. Virol. 82 (7) (2008) 3220–3235.
[26] I. Widjaja, C. Wang, R. van Haperen, J. Gutiérrez-Álvarez, B. van Dieren, N.M. Okba, V.S. Raj, W. Li, R. Fernandez-Delgado, F. Grosveld, Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein, Emerg. Microbes Infect. 8 (1) (2019) 516–530.
[27] C. Wang, W. Li, D. Drabek, N.M. Okba, R. van Haperen, A.D. Osterhaus, F.J. van Kuppeveld, B.L. Haagmans, F. Grosveld, B.-J. Bosch, A human monoclonal antibody blocking SARS-CoV-2 infection, Nat. Commun. 11 (1) (2020) 1–6.
[28] E.A. Van Erp, W. Luytjes, G. Ferwerda, P.B. Van Kasteren, Fc-mediated antibody effector functions during respiratory syncytial virus infection and disease, Front. Immunol. 10 (2019).
[29] B.M. Gunn, W.-H. Yu, M.M. Karim, J.M. Brannan, A.S. Herbert, A.Z. Wec, P.J. Halfmann, M.L. Fusco, S.L. Schendel, K. Gangavarapu, A role for Fc function in therapeutic monoclonal antibody-mediated protection against Ebola virus, Cell Host Microbe 24 (2) (2018).
[30] Y. Cheng, R. Wong, Y. Soo, W. Wong, C. Lee, M. Ng, P. Chan, K. Wong, C. Leung, G. Cheng, Use of convalescent plasma therapy in SARS patients in Hong Kong, Eur. J. Clin. Microbiol. Infect. Dis. 24 (1) (2005) 44–46.
[31] B. Zhou, N. Zhong, Y. Guan, Treatment with convalescent plasma for influenza A (H5N1) infection, New Engl. J. Med. 357 (14) (2007) 1450–1451.
[32] I.F. Hung, K.K. To, C.-K. Lee, K.-L. Lee, K. Chan, W.-W. Yan, R. Liu, C.-L. Watt, W.-M. Chan, K.-Y. Lai, Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection, Clin. Infect. Dis. 52 (4) (2011) 447–456.
[33] J.-H. Ko, H. Seok, S.Y. Cho, Y.E. Ha, J.Y. Baek, S.H. Kim, Y.-J. Kim, J.K. Park, C.R. Chung, E.-S. Kang, Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience, Antiviral Ther. 23 (7) (2018) 617–622.
[34] J. Mair-Jenkins, M. Saavedra-Campos, J.K. Baillie, P. Cleary, F.-M. Khaw, W.S. Lim, S. Makki, K.D. Rooney, C.P.S. Group, J.S. Nguyen-Van-Tam, The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis, J. Infect. Dis. 211(1) (2015) 80–90.
[35] J. Van Griensven, T. Edwards, X. de Lamballerie, M.G. Semple, P. Gallian, S. Baize, P.W. Horby, H. Raoul, N.F. Magassouba, A. Antierens, Evaluation of convalescent plasma for Ebola virus disease in Guinea, New Engl. J. Med. 374 (1) (2016) 33–42.
[36] P.-I. Lee, P.-R. Hsueh, Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV, J. Microbiol. Immunol. Infect. (2020).
[37] A. Casadevall, L.-A. Pirofski, The convalescent sera option for containing COVID-19, J. Clin. Invest. 130 (4) (2020) 1545–1548.
[38] L.C. Katzelnick, L. Gresh, M.E. Halloran, J.C. Mercado, G. Kuan, A. Gordon, A. Balmaseda, E. Harris, Antibody-dependent enhancement of severe dengue disease in humans, Science 358 (6365) (2017) 929–932.
[39] K. Duan, B. Liu, C. Li, H. Zhang, T. Yu, J. Qu, M. Zhou, L. Chen, S. Meng, Y. Hu, Effectiveness of convalescent plasma therapy in severe COVID-19 patients, Proc. Natl. Acad. Sci. 117 (17) (2020) 9490–9496.
[40] J. Liu, X. Zheng, Q. Tong, W. Li, B. Wang, K. Sutter, M. Trilling, M. Lu, U. Dittmer, D. Yang, Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV, J. Med. Virol. 92 (5) (2020) 491–494.
[41] J. Gong, H. Dong, S.Q. Xia, Y.Z. Huang, D. Wang, Y. Zhao, W. Liu, S. Tu, M. Zhang, Q. Wang, Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia, MedRxiv (2020).
[42] B. Li, F. Feng, G. Yang, A. Liu, N. Yang, Q. Jiang, H. Zhang, T. Wang, P. Li, Y. Mao, Immunoglobulin G/M and cytokines detections in continuous sera from patients with novel coronaviruses (2019-nCoV) infection, Available at SSRN 3543609 (2020).
[43] Y. Zhou, B. Fu, X. Zheng, D. Wang, C. Zhao, Pathogenic T cells and inflammatory

monocytes incite inflammatory storm in severe COVID-19 patients, Natl. Sci. Rev. (2020).

[44] Y. Yang, C. Shen, J. Li, J. Yuan, M. Yang, F. Wang, G. Li, Y. Li, L. Xing, L. Peng, Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome, MedRxiv (2020).

[45] H.-Y. Zheng, M. Zhang, C.-X. Yang, N. Zhang, X.-C. Wang, X.-P. Yang, X.-Q. Dong, Y.-T. Zheng, Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients, Cell. Mol. Immunol. (2020) 1–3.

[46] S. Wan, Q. Yi, S. Fan, J. Lv, X. Zhang, L. Guo, C. Lang, Q. Xiao, K. Xiao, Z. Yi, Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP), MedRxiv (2020).

[47] C. Zhang, Z. Wu, J.-W. Li, H. Zhao, G.-Q. Wang, The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality, Int. J. Antimicrob. Agents (2020) 105954.

[48] J. Stebbing, A. Phelan, I. Griffin, C. Tucker, O. Oechsle, D. Smith, P. Richardson, COVID-19: combining antiviral and anti-inflammatory treatments, The Lancet Infect. Dis. 20 (4) (2020) 400–402.

[49] R. Channappanavar, A.R. Fehr, R. Vijay, M. Mack, J. Zhao, D.K. Meyerholz, S. Perlman, Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice, Cell Host & Microbe 19 (2) (2016) 181–193.

[50] G. Cavalli, G. De Luca, C. Campochiaro, E. Della-Torre, M. Ripa, D. Canetti, C. Oltolini, B. Castiglioni, C.T. Din, N. Boffini, Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study, Lancet Rheumatol. (2020).

[51] L. Sun, M.C. Louie, K.M. Vannella, C.A. Wilke, A.M. LeVine, B.B. Moore, T.P. Shanley, New concepts of IL-10-induced lung fibrosis: fibrocyte recruitment and M2 activation in a CCL2/CCR2 axis, Am. J. Physiol.-Lung Cell. Mol. Physiol. 300 (3) (2011) L341–L353.

[52] T. Smith, J. Bushek, A. LeClaire, T. Prosser, COVID-19 Drug Therapy, Clinical Drug Information, Clinical Solutions (2020).

[53] J. Gao, Z. Tian, X. Yang, Breakthrough Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, Bioscience Trends (2020).

[54] N. Lee, K.A. Chan, D.S. Hui, E.K. Ng, A. Wu, R.W. Chiu, V.W. Wong, P.K. Chan, K. Wong, E. Wong, Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (4) (2004) 304–309.

[55] Y.-N. Ni, G. Chen, J. Sun, B.-M. Liang, Z.-A. Liang, The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis, Critical Care 23 (1) (2019) 99.

[56] S. Matsuyama, M. Kawase, N. Nao, K. Shirato, M. Ujike, W. Kamitani, M. Shimojima, S. Fukushi, The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15, bioRxiv (2020).

[57] D. Belhadi, N. Peiffer-Smadja, F.-X. Lescure, Y. Yazdanpanah, F. Mentré, C. Laouénan, A brief review of antiviral drugs evaluated in registered clinical trials for COVID-19, medRxiv (2020).

[58] A. Tahvildari, M. Arbabi, Y. Farsi, P. Jamshidi, S. Hasanzadeh, T.M. Calcagno, M.J. Nasiri, M. Mirsaeidi, Clinical features, Diagnosis, and Treatment of COVID-19: A systematic review of case reports and case series, medRxiv (2020).

[59] C. Wu, X. Chen, Y. Cai, X. Zhou, S. Xu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Internal Med. (2020).

[60] K. Iwabuchi, K. Yoshie, Y. Kurakami, K. Takahashi, Y. Kato, T. Morishima, Therapeutic potential of ciclesonide inahalation for COVID-19 pneumonia: report of three cases, J. Infect. Chemother. (2020).

[61] M. Khatri, L.A. Richardson, T. Meulia, Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model, Stem Cell Res. Therapy 9 (1) (2018) 1–13.

[62] A. Golchin, T.Z. Farahany, Biological products: cellular therapy and FDA approved products, Stem Cell Rev. Reports 15 (2) (2019) 166–175.

[63] J. Ankrum, Can cell therapies halt cytokine storm in severe COVID-19 patients? Sci. Transl. Med. 12 (540) (2020).

[64] A. Golchin, T.Z. Farahany, A. Khojasteh, F. Soleimanifar, A. Ardeshirylajimi, The clinical trials of mesenchymal stem cell therapy in skin diseases: an update and concise review, Curr. Stem Cell Res. Therapy 14 (1) (2019) 22–33.

[65] P. Mehta, D. Mcauley, M. Brown, E. Sanchez, R. Tattersall, J. Manson, S. Collaboration, Correspondence COVID-19: consider cytokine storm syndromes and, Lancet 6736(20) (2020) 19–20.

[66] A.R.R. Weiss, M.H. Dahlke, Immunomodulation by mesenchymal stem cells (MSCs): mechanisms of action of living, apoptotic, and dead MSCs, Front. Immunol. 10 (2019).

[67] J.D. Glenn, K.A. Whartenby, Mesenchymal stem cells: emerging mechanisms of immunomodulation and therapy, World J. Stem Cells 6 (5) (2014) 526.

[68] J. Chen, C. Hu, L. Chen, L. Tang, Y. Zhu, X. Xu, L. Chen, H. Gao, X. Lu, L. Yu, Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment, Engineering (2020).

[69] B. Liang, J. Chen, T. Li, H. Wu, W. Yang, Y. Li, J. Li, C. Yu, F. Nie, Z. Ma, Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells, ChinaXiv 2 (2020) v1.

[70] Z. Leng, R. Zhu, W. Hou, Y. Feng, Y. Yang, Q. Han, G. Shan, F. Meng, D. Du,

[71] S. Wang, Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, Aging Dis 11 (2) (2020) 216–228.

[71] P. Colson, J.-M. Rolain, J.-C. Lagier, P. Brouqui, D. Raoult, Chloroquine and hydroxychloroquine as available weapons to fight COVID-19, Int. J. Antimicrob. Agents 105932 (10.1016) (2020).

[72] T. Smith, T. Prosser, COVID-19 Drug Therapy-Potential Options, Elsevier, Amsterdam, 2020.

[73] X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, E. Dong, C. Song, In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Clin. Infect. Dis. (2020).

[74] S. Liu, C. Lien, P. Selveraj, T. Wang, Evaluation of 19 antiviral drugs against SARS-CoV-2 Infection, BioRxiv (2020).

[75] A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano, S. Einav, A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, J. Critical Care (2020).

[76] A. Shamshirian, A. Hessami, K. Heydari, R. Alizadeh-Navaei, M.A. Ebrahimzadeh, W.Y. George, R. Ghasemian, M. Behnamfar, H. Baradaran, E. Aboufazeli, Hydroxychloroquine versus COVID-19: a periodic systematic review and meta-analysis, MedRxiv (2020).

[77] P. Gautret, J.-C. Lagier, P. Parola, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V.E. Vieira, H.T. Dupont, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents (2020) 105949.

[78] L. Davidson, S. Canelon, M.R. Boland, Is hydroxychloroquine safe during pregnancy? Observations from penn medicine, medRxiv (2020).

[79] S.A. Lother, M. Abassi, A. Agostinis, A.S. Bangdiwala, M.P. Cheng, G. Drobot, N. Engen, K.H. Hullsiek, L.E. Kelly, T.C. Lee, Post-exposure prophylaxis or pre-emptive therapy for SARS-Coronavirus-2: study protocol for a pragmatic randomized controlled trial, medRxiv (2020).

[80] J. Geleris, Y. Sun, J. Platt, J. Zucker, M. Baldwin, G. Hripcsak, A. Labella, D. Manson, C. Kubin, R.G. Barr, Observational study of hydroxychloroquine in hospitalized patients with Covid-19, New Engl. J. Med. (2020).

[81] E.S. Rosenberg, E.M. Dufort, T. Udo, L.A. Wilberschied, J. Kumar, J. Tesoriero, P. Weinberg, J. Kirkwood, A. Muse, J. DeHovitz, Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state, JAMA (2020).

[82] C.P. Skipper, K.A. Pastick, N.W. Engen, A.S. Bangdiwala, M. Abassi, S.M. Lofgren, D.A. Williams, E.C. Okafor, M.F. Pullen, M.R. Nicol, Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial, Ann. Internal Med. (2020).

[83] O. Mitjà, M. Corbacho-Monné, M. Ubals, C. Tebe, J. Peñafiel, A. Tobias, E. Ballana, A. Alemany, N. Riera-Martí, C.A. Pérez, Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial, Clin. Infect. Dis. (2020).

[84] S. Arshad, P. Kilgore, Z.S. Chaudhry, G. Jacobsen, D.D. Wang, K. Huitsing, I. Brar, G.J. Alangaden, M.S. Ramesh, J.E. McKinnon, Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19, Int. J. Infect. Dis. (2020).

[85] M. Donoghue, F. Hsieh, E. Baronas, K. Godbout, M. Gosselin, N. Stagliano, M. Donovan, B. Woolf, K. Robison, R. Jeyaseelan, A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9, Circulation Res. 87 (5) (2000) e1–e9.

[86] I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol.: J. Pathol. Soc. Great Britain and Ireland 203 (2) (2004) 631–637.

[87] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C.-L. Hsieh, O. Abiona, B.S. Graham, J.S. McLellan, Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (6483) (2020) 1260–1263.

[88] Y. Wan, J. Shang, R. Graham, R.S. Baric, F. Li, Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus, J. Virol. 94 (7) (2020).

[89] V. Monteil, H. Kwon, P. Prado, A. Hagelkrüys, R.A. Wimmer, M. Stahl, A. Leopoldi, E. Garreta, C.H. Del Pozo, F. Prosper, Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2, Cell (2020).

[90] D. Batlle, J. Wysocki, K. Satchell, Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clin. Sci. 134 (5) (2020) 543–545.

[91] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (9) (2006).

[92] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, Jama (2020).

[93] M.E. Morra, L. Van Thanh, M.G. Kamel, A.A. Ghazy, A.M. Altibi, L.M. Dat, T.N.X. Thy, N.L. Vuong, M.R. Mostafa, S.I. Ahmed, Clinical outcomes of current medical approaches for Middle East respiratory syndrome: a systematic review and meta-analysis, Rev. Med. Virol. 28 (3) (2018) e1977.

[94] Y.M. Arabi, S. Shalhoub, Y. Mandourah, F. Al-Hameed, A. Al-Omari, E. Al Qasim, J. Jose, B. Alraddadi, A. Almotairi, K. Al Khatib, Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study, Clin. Infect. Dis. 70 (9) (2020) 1837–1844.

[95] A.A. Elfiky, Anti-HCV, nucleotide inhibitors, repurposing against COVID-19, Life Sci. 248 (2020) 117477.

[96] J.S. Khalili, H. Zhu, A. Mak, Y. Yan, Y. Zhu, Novel coronavirus treatment with ribavirin: Groundwork for evaluation concerning COVID-19, J. Med. Virol. (2020).

[97] L. Delang, R. Abdelnabi, J. Neyts, Favipiravir as a potential countermeasure against neglected and emerging RNA viruses, Antiviral Res. 153 (2018) 85–94.

[98] Q. Cai, M. Yang, D. Liu, J. Chen, D. Shu, J. Xia, X. Liao, Y. Gu, Q. Cai, Y. Yang, Experimental treatment with favipiravir for COVID-19: an open-label control study, Engineering (2020).

[99] C. Chen, J. Huang, Z. Cheng, J. Wu, S. Chen, Y. Zhang, B. Chen, M. Lu, Y. Luo, J. Zhang, Favipiravir versus arbidol for COVID-19: a randomized clinical trial, MedRxiv (2020).

[100] M.K. Lo, R. Jordan, A. Arvey, J. Sudhamsu, P. Shrivastava-Ranjan, A.L. Hotard, M. Flint, L.K. McMullan, D. Siegel, M.O. Clarke, GS-5734 and its parent nucleoside analog inhibit Filo- Pneumo-, and Paramyxoviruses, Sci. Rep. 7 (2017) 43395.

[101] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H.C. Hui, Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys, Nature 531 (7594) (2016) 381–385.

[102] M.K. Lo, F. Feldmann, J.M. Gary, R. Jordan, R. Bannister, J. Cronin, N.R. Patel, J.D. Klena, S.T. Nichol, T. Cihlar, Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge, Sci. Transl. Med. 11 (494) (2019) eaau9242.

[103] T.P. Sheahan, A.C. Sims, R.L. Graham, V.D. Menachery, L.E. Gralinski, J.B. Case, S.R. Leist, K. Pyrc, J.Y. Feng, I. Trantcheva, Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses, Sci. Transl. Med. 9 (396) (2017).

[104] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (3) (2020) 269–271.

[105] K.-T. Choy, A.Y.-L. Wong, P. Kaewpreedee, S.-F. Sia, D. Chen, K.P.Y. Hui, D.K.W. Chu, M.C.W. Chan, P.P.-H. Cheung, X. Huang, Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro, Antiviral Res. (2020) 104786.

[106] B. Williamson, F. Feldmann, B. Schwarz, K. Meade-White, D. Porter, J. Schulz, N. Van Doremalen, I. Leighton, C.K. Yinda, L. Pérez-Pérez, Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2, BioRxiv (2020).

[107] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, The Lancet (2020).

[108] Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment (2020).

[109] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M.-D. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the treatment of Covid-19 — preliminary report, New Engl. J. Med. (2020).

[110] A.G. Canga, A.M.S. Prieto, M.J.D. Liébana, N.F. Martínez, M.S. Vega, J.J.G. Vieitez, The pharmacokinetics and interactions of ivermectin in humans—a mini-review, AAPS J. 10 (1) (2008) 42–46.

[111] V. Götz, L. Magar, D. Dornfeld, S. Giese, A. Pohlmann, D. Höper, B.-W. Kong, D.A. Jans, M. Beer, O. Haller, Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import, Sci. Rep. 6 (1) (2016) 1–15.

[112] L. Lundberg, C. Pinkham, A. Baer, M. Amaya, A. Narayanan, K.M. Wagstaff, D.A. Jans, K. Kehn-Hall, Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication, Antiviral Res. 100 (3) (2013) 662–672.

[113] M. Tay, J.E. Fraser, W. Chan, N.J. Moreland, A.P. Rathore, C. Wang, S.G. Vasudevan, D.A. Jans, Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin, Antiviral Res. 99 (3) (2013) 301–306.

[114] K.M. Wagstaff, H. Sivakumaran, S.M. Heaton, D. Harrich, D.A. Jans, Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus, Biochem. J. 443 (3) (2012) 851–856.

[115] K.M. Wagstaff, S.M. Rawlinson, A.C. Hearps, D.A. Jans, An AlphaScreen®-based assay for high-throughput screening for specific inhibitors of nuclear import, J. Biomol. Screening 16 (2) (2011) 192–200.

[116] E. Mastrangelo, M. Pezzullo, T. De Burghgraeve, S. Kaptein, B. Pastorino, K. Dallmeier, X. de Lamballerie, J. Neyts, A.M. Hanson, D.N. Frick, Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug, J. Antimicrob. Chemother. 67 (8) (2012) 1884–1894.

[117] T.-L. Xu, Y. Han, W. Liu, X.-Y. Pang, B. Zheng, Y. Zhang, X.-N. Zhou, Antivirus effectiveness of ivermectin on dengue virus type 2 in Aedes albopictus, PLoS Neglected Trop. Dis. 12 (11) (2018) e0006934.

[118] L. Caly, J.D. Druce, M.G. Catton, D.A. Jans, K.M. Wagstaff, The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antiviral Res. (2020) 104787.

[119] S.N. Yang, S.C. Atkinson, C. Wang, A. Lee, M.A. Bogoyevitch, N.A. Borg, D.A. Jans, The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer, Antiviral Res. (2020) 104760.

[120] E. Yamasmith, P. Avirutnan, D. Mairiang, S. Tanrumluk, Y. Suputtamongkol, F. Saleh-arong, Efficacy and safety of ivermectin against dengue infection: a phase III, randomized, double-blind, placebo-controlled trial, He 34th Annual Meeting the Royal College of Physicians of Thailand. Internal Medicine and One Health, Chonburi, Thailand, 2018.

[121] O. Reynard, X.-N. Nguyen, N. Alazard-Dany, V. Barateau, A. Cimarelli, V.E. Volchkov, Identification of a new ribonucleoside inhibitor of Ebola virus replication, Viruses 7 (12) (2015) 6233–6240.

[122] N. Urakova, V. Kuznetsova, D.K. Crossman, A. Sokratian, D.B. Guthrie, A.A. Kolykhalov, M.A. Lockwood, M.G. Natchus, M.R. Crowley, G.R. Painter, β-D-N4-Hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome, J. Virol. 92 (3) (2018) e01965–e2017.

[123] M. Toots, J.D. Yoon, R.M. Cox, M. Hart, Z.M. Sticher, N. Makhsous, R. Plesker, A.H. Barrena, P.G. Reddy, D.G. Mitchell, Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia, Sci. Transl. Med. 11 (515) (2019).

[124] M.L. Agostini, A.J. Pruijssers, J.D. Chappell, J. Gribble, X. Lu, E.L. Andres, G.R. Bluemling, M.A. Lockwood, T.P. Sheahan, A.C. Sims, Small-molecule antiviral β-d-N4-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance, J. Virol. 93 (24) (2019).

[125] X. Lan, C. Shao, X. Zeng, Z. Wu, Y. Xu, Lopinavir-ritonavir alone or combined with arbidol in the treatment of 73 hospitalized patients with COVID-19: a pilot retrospective study, medRxiv (2020).

[126] Z. Zhu, Z. Lu, T. Xu, C. Chen, G. Yang, T. Zha, Y. Xue, Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, J. Infect. (2020).

[127] T.T. Yao, J.D. Qian, W.Y. Zhu, Y. Wang, G.Q. Wang, A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—a possible reference for coronavirus disease-19 treatment option, J. Med. Virol. (2020).

[128] Y. Deng, W. Liu, K. Liu, Y.Y. Fang, J. Shang, L. Zhou, K. Wang, F. Leng, S. Wei, L. Chen, H.G. Liu, Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study, Chinese Med. J. (2020).

[129] T. Li, H. Lu, W. Zhang, Clinical observation and management of COVID-19 patients, Emerg. Microb. Infect. 9 (1) (2020) 687–690.

[130] C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, J. Song, S. Wang, Y. Chao, Z. Yang, J. Xu, X. Zhou, D. Chen, W. Xiong, L. Xu, F. Zhou, J. Jiang, C. Bai, J. Zheng, Y. Song, Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 Pneumonia in Wuhan, China, JAMA Intern. Med. (2020).

[131] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, C. Clark, T. Iba, ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemost. 18 (5) (2020) 1023–1026.

[132] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. (2020).

[133] C.D. Barrett, H.B. Moore, M.B. Yaffe, E.E. Moore, ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment, J. Thromb. Haemost. (2020).

[134] M. Ranucci, A. Ballotta, U. Di Dedda, E. Bayshnikova, M. Dei Poli, M. Resta, M. Falco, G. Albano, L. Menicanti, The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome, J. Thromb. Haemost. (2020).

[135] B. Bikdeli, M.V. Madhavan, D. Jimenez, T. Chuich, I. Dreyfus, E. Driggin, C. Der Nigoghossian, W. Ageno, M. Madjid, Y. Guo, COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up, J. Am. College Cardiol. (2020).

[136] V.J.H.D. Brandon M. Parker, Rishi Rattan, Coagulopathy in COVID-19: review and recommendations (2020).

[137] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemost. 18 (5) (2020) 1094–1099.

[138] J. Liu, R. Cao, M. Xu, X. Wang, H. Zhang, H. Hu, Y. Li, Z. Hu, W. Zhong, M. Wang, Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro, Cell Discov. 6 (1) (2020) 1–4.

[139] Z. Chen, J. Hu, Z. Zhang, S. Jiang, S. Han, D. Yan, R. Zhuang, B. Hu, Z. Zhang, Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial, MedRxiv (2020).

[140] E.S. Rosenberg, E.M. Dufort, T. Udo, L.A. Wilberschied, J. Kumar, J. Tesoriero, P. Weinberg, J. Kirkwood, A. Muse, J. DeHovitz, D.S. Blog, B. Hutton, D.R. Holtgrave, H.A. Zucker, Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State, JAMA (2020).

[141] E.K. McCreary, J.M. Pogue, Coronavirus disease 2019 treatment: a review of early and emerging options, Open Forum Infectious Diseases, Oxford University Press US, 2020, p. ofaa105.

[142] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, Compassionate use of remdesivir for patients with severe Covid-19, New Engl. J. Med. (2020).

[143] T.P. Sheahan, A.C. Sims, S. Zhou, R.L. Graham, A.J. Pruijssers, M.L. Agostini, S.R. Leist, A. Schäfer, K.H. Dinnon, L.J. Stevens, An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice, Sci. Transl. Med. 12 (541) (2020).

[144] Q.-L. Zeng, Z.-J. Yu, J.-J. Gou, G.-M. Li, S.-H. Ma, G.-F. Zhang, J.-H. Xu, W.-B. Lin, G.-L. Cui, M.-M. Zhang, Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients, J. Infect. Dis. (2020).

[145] M. Ye, D. Fu, Y. Ren, F. Wang, D. Wang, F. Zhang, X. Xia, T. Lv, Treatment with convalescent plasma for COVID-19 patients in Wuhan, China, J. Med. Virol. (2020).

[146] X. Xu, M. Han, T. Li, W. Sun, D. Wang, B. Fu, Y. Zhou, X. Zheng, Y. Yang, X. Li, Effective treatment of severe COVID-19 patients with tocilizumab, Proc. Natl. Acad. Sci. 117 (20) (2020) 10970–10975.

[147] P. Luo, Y. Liu, L. Qiu, X. Liu, D. Liu, J. Li, Tocilizumab treatment in COVID-19: a single center experience, J. Med. Virol. (2020).

[148] F. Alberici, E. Delbarba, C. Manenti, L. Econimo, F. Valerio, A. Pola, C. Maffei, S. Possenti, N. Zambetti, M. Moscato, A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients

admitted for SARS-CoV2 pneumonia, Kidney Int. (2020).

[149] A. Gasmi, S. Noor, T. Tippairote, M. Dadar, A. Menzel, G. Bjørklund, Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic, Clin. Immunol. (2020) 108409.

[150] G. Gritti, F. Raimondi, D. Ripamonti, I. Riva, F. Landi, L. Alborghetti, M. Frigeni, M. Damiani, C. Micò, S. Fagiuoli, Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support, MedRxiv (2020).

[151] Y. Wang, W. Jiang, Q. He, C. Wang, B. Wang, P. Zhou, N. Dong, Q. Tong, Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China, medRxiv (2020).

[152] F. Cantini, L. Niccoli, D. Matarrese, E. Nicastri, P. Stobbione, D. Goletti, Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact, J. Infect. (2020).

[153] L. Fang, G. Karakiulakis, M. Roth, Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Resp. Med. (2020).

[154] C. Amici, A. Di Coro, A. Ciucci, L. Chiappa, C. Castilletti, V. Martella, N. Decaro, C. Buonavoglia, M.R. Capobianchi, M.G. Santoro, Indomethacin has a potent antiviral activity against SARS coronavirus, Antiviral Therapy 11 (8) (2006) 1021.

[155] E.L. Tan, E.E. Ooi, C.-Y. Lin, H.C. Tan, A.E. Ling, B. Lim, L.W. Stanton, Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs, Emerg. Infect. Dis. 10 (4) (2004) 581.

[156] J.H. Beigel, H.H. Nam, P.L. Adams, A. Krafft, W.L. Ince, S.S. El-Kamary, A.C. Sims, Advances in respiratory virus therapeutics–A meeting report from the 6th isirv Antiviral Group conference, Antiviral research (2019).

[157] N. Yamamoto, S. Matsuyama, T. Hoshino, N. Yamamoto, Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro, bioRxiv (2020).

[158] N. Fintelman-Rodrigues, C.Q. Sacramento, C.R. Lima, F.S. da Silva, A. Ferreira, M. Mattos, C.S. de Freitas, V.C. Soares, S.d.S.G. Dias, J.R. Temerozo, Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production, bioRxiv (2020).

[159] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19, New Engl. J. Med. (2020).

[160] L. Deng, C. Li, Q. Zeng, X. Liu, X. Li, H. Zhang, Z. Hong, J. Xia, Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study, J. Infect. (2020).