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Contents

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REVIEW

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Contents

ABOUT COVER

Editorial Board Member of the *World Journal of Virology*, Celso Cunha holds a PhD in Biology (awarded 1992) and is currently Associate Professor of Habilitation in the Institute of Hygiene and Tropical Medicine at NOVA University (IHMT-NOVA; Lisbon, Portugal). In his professional career, his academic and administrative duties have included coordination of a Master's Program in Biomedical Sciences and membership on the scientific committees for two PhD Programs. In addition to his ongoing leadership of a research group focusing on host-pathogen interactions in hepatitis B and D infections at IHMT-NOVA, he also serves as Director of the Institute's Medical Microbiology Unit and as a member of the Institute's Counsel. Outside of the IHMT-NOVA, he serves on several evaluation panels for various international agencies related to his research interests. (L-Editor: Filipodia)

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The primary aim of *World Journal of Virology* (*WJV*, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

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REVIEW

Emerging therapeutics in the management of COVID-19

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Abstract

The severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019, COVID-19) pandemic has placed a tremendous burden on healthcare systems globally. Therapeutics for treatment of the virus are extremely inconsistent due to the lack of time evaluating drug efficacy in clinical trials. Currently, there is a deficiency of published literature that comprehensively discusses all therapeutics being considered for the treatment of COVID-19. A review of the literature was performed for articles related to therapeutics and clinical trials in the context of the current COVID-19 pandemic. We used PubMed, Google Scholar, and Clinicaltrials.gov to search for articles relative to the topic of interest. We used the following keywords: "COVID-19", "therapeutics", "clinical trials", "treatment", "FDA", "ICU", "mortality", and "management". In addition, searches through the references of retrieved articles was also performed. In this paper, we have elaborated on the therapeutic strategies that have been hypothesized or trialed to-date, the mechanism of action of each therapeutic, the clinical trials finished or in-

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process that support the use of each therapeutic, and the adverse effects associated with each therapeutic. Currently, there is no treatment that has been proven to provide significant benefit in reducing morbidity and mortality. There are many clinical trials for numerous different therapeutic agents currently underway. By looking back and measuring successful strategies from previous pandemics in addition to carrying out ongoing research, we provide ourselves with the greatest opportunity to find treatments that are beneficial.

Key Words: COVID-19; Therapeutics; Infectious disease; SARS-CoV-2; Pharmacology; Virology

Core Tip: As coronavirus disease 2019 continues to affect the global community, researchers are working diligently to determine the efficacy of therapeutic agents to fight this virus in clinical trials. Currently, there is a lack of published literature that comprehensively discusses all of the therapeutic agents under investigation. In this manuscript, we provide readers with a thorough and comprehensive evaluation of the current state of therapeutics including the proposed mechanisms of action, pharmacokinetics, recommended dosages, adverse effects, and efficacy data from clinical trials.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), a disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been labelled a pandemic by the World Health Organization after its emergence from Wuhan, Hubei Province, China in December 2019. It has since infected more than 60 million people worldwide. The presentation of the disease varies, however the most common symptoms include fever, cough, and dyspnea[1-3]. Other possible symptoms include rhinorrhea, sore throat, headache, gastrointestinal (GI) disturbances, and fatigue[3]. Because of the extensive morbidity and mortality related to COVID-19 infection, researchers and clinicians are racing to find effective therapeutics for the treatment of this disease. On March 28, 2020 the United States Federal Drug Administration (FDA) issued an emergency authorization for chloroquine (CQ) phosphate and hydroxychloroquine (HCQ) sulfate as a treatment for adults and adolescents weighing greater than 50 kg, who are hospitalized, and for whom a clinical trial is not available or feasible[4]. Furthermore, on May 1, 2020 an emergency authorization was issued for Remdesivir to be used for adults and children with severe disease, defined as SpO_2 less than 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)[4]. Clinical trials for numerous therapeutics are on-going worldwide. In this review, we will familiarize readers with the current therapeutics being investigated for the treatment of COVID-19, including their mechanisms of action, rationale for use, adverse effects, and information from clinical trials in the currently published literature. A summary of the therapeutics can be found in monoclonal antibodies (Table 1), antivirals (Table 2), cell and RNA-based therapies (Table 3) and miscellaneous treatment (Table 4).

METHODS

A literature review was performed for articles related to therapeutics and clinical trials

Table 1 Monoclonal antibodies (a survey)

Drug	Current use/FDA approval	Proposed mechanism of action	Published trials
Sarilumab	FDA approved for use in rheumatoid arthritis	Monoclonal antibody, IL-6 receptor antagonist	(1) Sanofi and Regeneron [10]; (2) Benucci *et al*[11]; and (3) See Clinicaltrials.gov for ongoing trials
Siltuximab	FDA Approved for use in Multicentric Castleman's disease	Monoclonal antibody, IL-6 receptor antagonist	(1) Gritti *et al*[14]; and (2) See Clinicaltrials.gov for ongoing trials
Leronlimab	Not currently FDA approved, however under investigation for COVID-19 and HIV	Monoclonal antibody, CCR5 antagonist	(1) CytoDyn [17]; and (2) See Clinicaltrials.gov for ongoing trials
PD-1 inhibitors	FDA approved for the treatment of various malignancies	Inhibition of PD-1 pathway	No currently published trials
Gimsilumab	Not currently FDA approved. Clinical Trials are underway testing Gimsilumab as a treatment for ankylosing spondylitis as well as ARDS	Monoclonal antibody against GM-CSF	See Clinicaltrials.gov for ongoing trials

FDA: Federal Drug Administration; IL: Interleukin; COVID-19: Coronavirus disease 2019; HIV: Human immunodeficiency virus; PD-1: Programmed cell death protein 1; GM-CSF: Granulocyte macrophage colony stimulating factor; ARDS: Acute respiratory distress syndrome.

Table 2 Antivirals (a survey)

Drug	Current use/FDA approval	Proposed mechanism of action	Published trials
Arbidol	Approved in other countries for influenza treatment and prophylaxis, however not approved in the United States	Antiviral, inhibits viral-mediated fusion with target membrane, blocking viral entry into target cells	Zhang *et al*[38]
ASC09	Not currently FDA approved. Trials are underway testing ASC09 as a treatment for HIV and COVID-19	Antiviral, Protease inhibitor	See Clinicaltrials.gov for ongoing trials
Azvudine	Currently being tested in clinical trials for HIB and COVID-19	Antiviral, nucleoside reverse transcriptase inhibitor	See Clinicaltrials.gov for ongoing trials
Favipravir	Approved in other countries for the treatment of influenza, however not FDA approved in the United States	Antiviral, Inhibits RNA-dependent RNA polymerase	(1) Cai *et al*[52]; (2) Chen *et al*[33]; and (3) See Clinicaltrials.gov for ongoing trials
Baloxavir marboxil	Approved for treatment of uncomplicated influenza A and B in individuals age 12 and older who have been symptoms for no more than 48 h	Antiviral, cap-dependent endonuclease inhibitor	Lou *et al*[59]
Remdesivir	FDA Emergency Use Authorization for COVID-19	Antiviral, inhibitor of RNA-dependent RNA polymerase	(1) Wang *et al*[68]; (2) NIH (ACTT trial)[69]; (3) Beigel *et al*[71]; and (4) See Clinicaltrials.gov for ongoing trials

FDA: Federal Drug Administration; COVID-19: Coronavirus disease 2019; HIV: Human immunodeficiency virus; NIH: National Institutes of Health; ACTT: Adaptive COVID-19 Treatment Trial.

in the context of the current COVID-19 pandemic. We used PubMed, Google Scholar, and Clinicaltrials.gov to search for articles relative to the topic of interest. We used the following keywords: "COVID-19", "therapeutics", "clinical trials", "treatment", "FDA", "ICU", "mortality", and "management". In addition, searches through the references of retrieved articles was also performed. Three reviewers were responsible for performing article selection based on relevance to our topic. Inclusion criteria included both published and pre-published works that were available in English, and articles related to therapeutics and clinical trials for COVID-19 in all settings. We excluded abstracts, non-English articles, and those unrelated to therapeutics and COVID-19.

MONOCLONAL ANTIBODIES

Sarilumab

Chemical composition: Sarilumab (Kevzara) is a fully human monoclonal antibody that acts as an interleukin (IL)-6 receptor antagonist, which leads to blockage of the

Table 3 Cell and RNA-based therapies

Drug	Current use/FDA approval	Proposed mechanism of action	Published trials
Mesenchymal stem cells	FDA approved for graft versus host disease	Prevention of cytokine release as well as promotion of cellular repair/regeneration	(1) Leng *et al*[75]; and (2) See Clinicaltrials.gov for ongoing trials
MultiStem	Currently being studied for treatment of ischemic stroke, ulcerative colitis, acute myocardial infarction, and graft *vs* host disease	Immune system modulation, anti-inflammatory, pro-angiogenic	See Clinicaltrials.gov for ongoing trials
RNA based therapies	Have been utilized as anticancer and antiviral therapy. Have also been implemented in genetic diseases	Interfere with gene expression through RNA interference	See Clinicaltrials.gov for ongoing trials

FDA: Federal Drug Administration.

Table 4 Miscellaneous therapeutics

Drug	Current use/FDA approval	Proposed mechanism of action	Published trials
APN01	Known to have anti-hypertensive and anti-neoplastic properties	Cleaves angiotensin II to form angiotensin-1-7	See Clinicaltrials.gov for ongoing trials
Chloroquine/hydroxychloroquine	Anti-malarial, anti-viral, and anti-rheumatic effects. Previous studied in the 2004 SARS outbreak	Poorly understood. Likely mechanism includes accumulation of basic drug in lysosomes, altering pH and disrupting enzymes involved in post-translation protein modification	(1) Gautret *et al*[105]; (2) Tang *et al*[107]; (3) Borba *et al*[108]; (4) Horby *et al*[109]; and (5) Boulware *et al*[110]
Azithromycin	Macrolide antibiotic, classically using in the treatment of several bacterial infectious processes	Bacteriostatic properties due to binding of the 50 s ribosomal subunit, inhibiting bacterial protein synthesis. Against SARS-CoV-2, it is hypothesized that intracellular accumulation alters pH, leading to interference with viral activities	(1) All trials have been performed using Azithromycin as an adjunct to CQ/HCQ; and (2) No clinical trials evaluating the efficacy of azithromycin alone
Colchicine	Treatment for gout. Implicated in familial Mediterranean fever, primary biliary cirrhosis, psoriasis, sarcoidosis, scleroderma, amyloidosis, pericarditis, Sweet syndrome, and Behcet disease	Anti-inflammatory agent, binds to beta-tubulin in neutrophils leading to inhibition of assembly and polymerization of microtubules. This leads to decrease in several neutrophilic inflammatory processes	Gendelman *et al*[123]
Corticosteroids/methylprednisolone	Used in a variety of clinical instances as anti-inflammatory agents	Extensive anti-inflammatory and anti-fibrotic properties, thought to decrease inflammation	(1) Wu *et al*[135]; (2) Wang *et al*[133]; and (3) Horby *et al*[136]
Ivermectin	Used as an anti-parasitic agent, however has shown antiviral activity against numerous pathogens	May play a role in inhibiting viral nuclear import into the host cell *via* interactions with IMPalpha/B1	Caly *et al*[143]
Convalescent plasma	Has been used in previous pandemics, including SARS, MERS, Ebola, and H1N1 for the purpose of passive immunization	By sharing plasma of individuals who have previously been infected, passive immunization occurs	(1) Li *et al*[148]; (2) Shen *et al*[149]; and (3) Duan *et al*[150]
ECMO	Used to support cardiac and pulmonary function in critically ill patients	Assists the cardiorespiratory system functioning in patients with severe ARDS	Currently, no randomized clinical trials have evaluated the efficacy of using ECMO in the treatment of COVID-19

FDA: Federal Drug Administration; COVID-19: Coronavirus disease 2019; SARS: Severe acute respiratory syndrome; ECMO: Extracorporeal membrane oxygenation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ARDS: Acute respiratory distress syndrome; CQ: Chloroquine; HCQ: Hydroxychloroquine.

development of IL-6 mediated inflammation[5]. It is currently best known for its role in the treatment of rheumatoid arthritis. It is a covalent heterotetramer made up of two disulfide linked heavy chains linked to a kappa light chain[6].

Mechanism of action: The proposed mechanism of action of Sarilumab against COVID-19 is due to its ability to act as an IL-6 receptor antagonist[7]. It has been demonstrated that patients with severe COVID-19 infection are more likely to have elevated levels of several biomarkers, including IL-6[8]. The binding of SARS-CoV-2 to

the alveolar epithelial cells leads to the activation of the innate and adaptive immune systems, which leads to the production of several pro-inflammatory cytokines[7]. IL-6 promotes T-cell activation, B-cell differentiation, and induces the production of acute phase reactants from the liver[7]. In addition, elevated levels of IL-6 have been associated with cardiovascular diseases such as atherosclerosis, heart failure, angina, and hypertension[7].

Pharmacokinetics: Sarilumab is shown to be well absorbed in Rheumatoid Arthritis patients[6]. In one study of the pharmacokinetics of Sarilumab in 1770 patients with rheumatoid arthritis, 631 patients received 150 mg and 682 patients received 200 mg of Sarilumab every two weeks for up to one year[6]. On average, Tmax was observed between 2 to 4 d[6]. The volume of distribution at steady state is 7.3 L[6]. As with other monoclonal antibodies, it is believed to be degraded into peptides and amino acids[6]. It is not eliminated by either the hepatic or renal systems, but rather it is eliminated predominately through proteolytic pathways[6].

Adverse effects: There is limited clinical trial data available describing the adverse effects of Sarilumab for the treatment of COVID-19. A review of the use of Sarilumab in the treatment of rheumatoid arthritis along with other disease modifying antirheumatic drugs (DMARDs) found that neutropenia (9.8% to 14.2%), upper respiratory infections (6.4% to 7.1%), elevated alanine aminotransferase (ALT) (6.7% to 6.8%), and local injection site erythema (5.3%) were some of the more common side effects[9]. When Sarilumab was used as monotherapy, neutropenia (15.6%), nasopharyngitis (6%), and injection site erythema (6.2%) were among the most common side effects[9].

Dosage: Published clinical trial data for Sarilumab is lacking. Current unpublished data available has suggested using either 200 mg or 400 mg intravenous doses, depending on the study protocol[10,11].

Randomized clinical trials: There are no currently published clinical trials demonstrating efficacy for Sarilumab in the treatment of COVID-19. However, a large phase 2/3, randomized placebo-controlled study of Sarilumab in hospitalized patients with severe COVID-19 is ongoing[10]. In addition, a case series by Benucci *et al*[11] described the clinical course of eight patients hospitalized in Italy with COVID-19. Patients were given 400 mg of Sarilumab in addition to HCQ, azithromycin, darunavir, cobicistat, and enoxaparin at 24 h after hospitalization[11]. An additional 200 mg dose was given to patients after 48 and 96 h, respectively. In this series, 7 patients saw substantial improvements in their SpO_2/FiO_2 ratio and were discharged home after testing negative for COVID-19 within 14 d[11]. Only 1 of the patients, who was 83 years old, died after 13 d[11]. Further clinical trials are needed to evaluate the efficacy and safety of Sarilumab for the treatment of COVID-19.

Siltuximab

Chemical composition: Siltuximab (Sylvant) is a chimeric monoclonal antibody that acts *via* inhibition of IL-6, similar to Sarilumab[12]. It is known for its role in treating a variety of malignancies, including multicentric Castleman's disease, multiple myeloma, myelodysplastic syndrome, prostate cancer, ovarian cancer, and lung cancer[12].

Mechanism of action: The primary mechanism of Siltuximab is *via* binding to and/or neutralization of IL-6[12]. As discussed previously, IL-6 is a proinflammatory cytokine that has been shown to be elevated in patients suffering from severe COVID-19[8].

Pharmacokinetics: Siltuximab is primarily distributed within the intravascular space[13]. It is approved in the United States to be given at doses of 11 mg/kg over the course of a one hour infusion once every three weeks[13]. The steady state is reached by the sixth dose, accumulating at 1.7 times higher than the concentration achieved *via* a single dose[13]. The volume of distribution in a 75 kg man is approximately 4.5 L, and the half-life is approximately 20.6 d[13]. It is cleared *via* first order elimination at a rate of 0.23 L per day[13].

Profit and adverse effects: The safety and efficacy of Siltuximab in the treatment of COVID-19 has not yet been established. Further clinical trials are needed to determine adverse effects of this medication. The most common adverse effects of Siltuximab therapy when used for the purposes of treating Castleman's disease and Multiple Myeloma include weight gain, hyperuricemia, respiratory infections, rash, and

pruritus[12].

Dosage: In the only clinical trial currently reported from Italy, patients received the standard dose of Siltuximab, 1 1mg/kg IV infusion over the course of one hour[14]. In addition, a second dose was able to be given at the physician's discretion[14].

Randomized clinical trials: Currently, there is no published data regarding the usage of Siltuximab for the treatment of COVID-19. Currently, an unpublished study from Italy evaluated the use of Siltuximab in 21 patients admitted to the hospital with confirmed COVID-19[14]. All of the patients who were available for follow up had CRP levels normalized (median time to follow up = 8 d). Additionally, 7 patients experienced a reduced need for ventilation, 9 patients experienced clinical stabilization of their position, while 5 patients experienced worsening of their condition described as the need for intubation during the course of the study[14].

Leronlimab (PRO 140)

Chemical composition: Leronlimab is a humanized immunoglobulin (Ig) G4 monoclonal antibody that acts as a CCR5 antagonist[15]. It is currently in clinical trials for the treatment of human immunodeficiency virus (HIV)[15].

Mechanism of action: Leronlimab is a CCR5 receptor antagonist. CCR5 is a fusion co-receptor used by the HIV-1 virion to enter into human cells[16]. It is thought that the CCR5 receptor plays a role in immune cell trafficking to sites of inflammation, and for this reason there is a potential benefit for the use of this drug in the treatment of COVID-19[17].

Pharmacokinetics: A clinical trial by Jacobson *et al*[18] examined the use of Leronlimab in the treatment of HIV. Subjects were given either placebo, a 162 mg dose, or a 324 mg dose of Leronlimab weekly for three weeks[18]. The average peak concentration of the drug was 6.1 mg/L and 13.8 mg/L for the 162 mg group and the 324 mg group, respectively[18]. The average half-life was 3.4 and 3.7 d for each respective group[18]. There is little information available regarding the metabolism and elimination of Leronlimab.

Adverse effects: There are no documented adverse effects regarding the use of Leronlimab in the treatment of COVID-19. Jacobson *et al*[18] found in their study that the most frequent adverse effects of Leronlimab in the treatment of HIV included diarrhea (14%), headache (14%), lymphadenopathy (11%), and hypertension (9%).

Randomized clinical trials: Currently, no published randomized clinical trials have evaluated the use of Leronlimab in the treatment of COVID-19. However, in New York, 10 severely ill patients with COVID-19 have received treatment with Leronlimab[17]. After three days, eight of these patients showed significant improvement in levels of cytokines, including IL-6, as well as improvements in CD4/CD8 T-cell ratios[17]. Currently, patients are enrolling in Phase 2 and Phase 2b/3 trials for the use of Leronlimab in the treatment of severe COVID-19[17].

Programmed cell death inhibitors

Chemical composition: Antibodies that block programmed cell death (PD-1) are known as immune checkpoint inhibitors. Immune checkpoints refer to inhibitory pathways that are crucial for maintaining self-tolerance and controlling the physiologic immune responses in peripheral tissues to minimize tissue damage when responding to pathogenic infections. Many immune checkpoints are initiated by ligand-receptor binding, which allows for blockade by antibodies[19].

Mechanism of action: When PD-1 binds to its ligand (PD-L1), it has an immunosuppressive effect[19]. PD-1 and its ligands have traditionally been studied for antitumor treatment because of the ability of cancer to dysregulate the expression of these checkpoint proteins, which allows it to escape T-cell mediated cell death.

Pharmacokinetics: The pharmacokinetics of immune checkpoint inhibitors like PD-1 blocking antibodies are impacted by time-varying clearance and the target-mediated drug position[20]. Differences in patient-specific characteristics only account for some of the variability in the pharmacokinetics of immune checkpoint inhibitors. Immune checkpoint inhibitors appear to have little to no impact on liver and renal function[20]. They display limited diffusion outside of the vascular space[20]. They have a long half-life and are cleared through a receptor-mediated mechanism in both linear and

nonlinear phases[20]. Clearance may occur through nonspecific degradation in tissues and plasma[21].

Adverse effects: There is currently no clinical trial data available describing the adverse effects of PD-1 blocking antibodies in the treatment of COVID-19. Previously reported adverse effects vary including the following disturbances: gastrointestinal (bloody diarrhea, abdominal pain, and pyrexia), hepatic (jaundice, and asymptomatic liver enzyme elevation), endocrine (hypophysitis, hypo/hyperthyroiditis, primary adrenal insufficiency, and hypercalcemia), skin (rash and Stevens-Johnson syndrome), rheumatological (mild arthralgia, myalgia, and arthritis), neurological, renal, pulmonary (pneumonitis), cardiac (myocarditis, myositis), and many others[22]. It should be noted that the incidence of these adverse effects varies[22]. In one smaller study of 19 patients receiving PD-1 therapy, some patients experienced flares of pre-existing autoimmune disease with treatment[23]. Similar results were also seen in patients receiving anti-PD-1 therapy in a larger, multicenter trial[24].

Dosage: There is limited data regarding dosing for the use of PD-1 inhibitors in the treatment of COVID-19. In one clinical trial, 200 mg of the PD-1 inhibitor Camrelizumab was administered one time intravenously[25].

Randomized clinical trials: There are no currently published randomized clinical trials regarding the use of PD-1 inhibitors in patients with COVID-19. Researchers at Southeast University in China are currently studying the efficacy of Camrelizumab in patients with severe pneumonia associated with lymphocytopenia in COVID-19 patients in order to restore immunoactivity[25].

Gimsilumab

Chemical composition: Gimsilumab (KIN-1901) is a fully human monoclonal antibody that antagonizes granulocyte macrophage colony stimulating factor (GM-CSF)[26]. This monoclonal antibody is fully human and is directed at a proinflammatory cytokine that is thought to play a role in autoimmunity and inflammation[26].

Mechanism of action: GM-CSF is a hematopoietic growth factor that can stimulate the proliferation of granulocytes and macrophages which can contribute to increased inflammation and cytokine release in COVID-19 patients[3]. It is found in synovial fluid in patients who have spondylarthritis; therefore, this drug has been studied in the setting of ankylosing spondylitis because it may neutralize the cytokine activity and benefit patients[26].

Pharmacokinetics: Because this drug is still under investigation and is relatively new, little information is available about the pharmacokinetics of Gimsilumab.

Adverse effects: There is currently no clinical trial data available describing the adverse effects of Gimsilumab in the treatment of COVID-19. Since the drug is still under investigation and is relatively new, little information is available about the adverse effects of Gimsilumab.

Dosage: Dosage information for Gimsilumab as a treatment for COVID 19 is not currently available. One study looking at Gimsilumab in the treatment of ankylosing spondylitis administered single or repeat subcutaneous injections once weekly for four weeks[26]. A trial for the use of Gimsilumab in patients with COVID-19 is planning to administer high dose Gimsilumab on day one and low dose on day eight of treatment, unless the patient is discharged or no longer in need of supplemental oxygen or ventilator support for over 48 h on day 8[27]. Unfortunately, specific information regarding what constitutes "high dose" and "low dose" is not available.

Randomized clinical trials: Gimsilumab was originally being studied as a treatment for ankylosing spondylitis and thus far a Phase 1 study has been completed which demonstrated a favorable safety and tolerability profile with no serious adverse events. However, because of its possible applicability in COVID-19, trials will be focused on the prevention of acute respiratory distress syndrome (ARDS) and cytokine storm instead of Phase 2 trials on rheumatic diseases[26]. It has been found that the percentage of GM-CSF expressing white blood cells are higher in the blood of intensive care unit (ICU)-admitted COVID-19 patients when compared to healthy controls, as well as non-ICU patients[28]. One study is examining the efficacy and safety of Gimsilumab in people with lung injury or ARDS secondary to COVID-19 infection in a randomized double blinded trial[27]. This study will have a 2-wk treatment period

and a 22-wk follow-up period[27].

ANTIVIRALS

Arbidol (umifenovir)

Chemical composition: Arbidol{ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate} is a broad-spectrum antiviral compound[29]. Although it has been used for the treatment and prevention of influenza in Russia and China for decades, it has not been approved for this purpose by the Food and Drug Administration in the United States[29].

Mechanism of action: The anti-viral mechanism involves inhibition of virus-mediated fusion with the target membrane and a resulting block of virus entry into target cells[30]. It inhibits viral glycoprotein conformational changes during membrane fusion by interacting with the phospholipid membrane and protein motifs enriched in aromatic residues[30].

Pharmacokinetics: Regarding metabolism, 33 metabolites of Arbidol have been identified in human plasma, urine, and feces[31]. The drug is rapidly absorbed when administered orally, with a t_{max} of 1.38 h[31]. The main biotransformation pathways of Arbidol are sulfoxidation, glucuronidation, sulfate conjugation, and dimethylamine N-demethylation[31]. The primary urine metabolites are glucuronide and sulfate conjugates[31]. The liver and intestines are primarily responsible for the metabolism of Arbidol in humans, with CYP3A4 being a major isoform and other P450 enzymes and flavin-containing monooxygenases playing less significant roles in metabolism[31]. It has a long elimination half-life, which is reported to be 25 h, and high plasma exposure[31].

Adverse effects: One study reported that 43.7% of patients had digestive upset, such as mild diarrhea and nausea, with Arbidol treatment[32]. In this study, however, no patients stopped treatment with Arbidol due to adverse effects[32]. Another study showed an increase in serum uric acid in 2.5% of patients taking Arbidol[33].

Dosage: Current recommendations for Arbidol dosing are as follows: 200mg orally 3 times a day for no more than 10 d in adults[34]. In clinical trials, 200 mg orally 3 times a day for 7-10 d or longer is currently being used and investigated[33,35-37].

Randomized clinical trials: Zhang *et al*[38] conducted a retrospective case-control study to evaluate the efficacy of Arbidol as a post-exposure prophylactic medication on family members and health care workers who were exposed to patients confirmed to have SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) and chest computed tomography (CT) scan. Logistic regression based on the data of the family members and health care workers with Arbidol or Oseltamivir prophylaxis showed that Arbidol post-exposure prophylaxis was protective against the development of COVID-19 [hazard ratio 0.025, 95% confidence interval (CI) 0.003-0.209, P = 0.0006 for family members and hazard ratio 0.056, 95%CI = 0.005-0.662, P = 0.0221 for health care workers][38]. They suggested Arbidol could reduce the infection risk of the novel coronavirus in hospital and family settings[38]. Though the study had a number of limitations and warrants further research, most healthcare facilities in China have already adopted the usage of Arbidol as a standard protocol for post-exposure prophylaxis of COVID-19 transmission among its healthcare workers.

ASC09

Chemical composition: ASC09, which is also referred to as TMC-310911, is not currently FDA approved for the treatment of COVID-19[39]. It is similar in structure to darunavir and is an investigational drug currently under study for use in HIV-1 infections as well as for treatment for COVID-19[40,41].

Mechanism of action: ASC09 is an HIV protease inhibitor[39]. Regarding HIV-1, the drug binds to the protease enzyme in order to inhibit the cleavage of Gag-Pol polyproteins and Gag polyproteins. This inhibition prevents the formation of mature virus particles capable of infection[40].

Pharmacokinetics: The drug is metabolized mainly by CYP enzymes[42]. The terminal

elimination half-life of ASC09 ranged from 1.25 to 3.751 h in one study. Multiple oral doses that ranged from 150 mg twice daily to 900 mg twice daily were also studied and showed that the terminal elimination ranged from 12.23 to 16.48 h[42].

Adverse effects: In one Phase IIa study the authors looked at the adverse effects of ASC09 in HIV patients[43]. The study found that the most common adverse events were fatigue and nausea, which occurred in at least 10% of the 33 participants[43]. Gastrointestinal-related adverse effects occurred in approximately 27% of participants[43]. No deaths or serious adverse events were reported. No adverse events resulted in patient discontinuation of the study. There were rises in liver enzymes in two patients, although the presence of cytomegalovirus hepatitis in one patient may have accounted for this abnormality[43].

Dosage: Dosage information for ASC09 as a treatment for COVID 19 is not currently available. One clinical trial planned to give ASC09/ritonavir in 300 mg/100 mg tablets twice daily for 14 d[44].

Randomized clinical trials: To date, there are no completed clinical trials evaluating the efficacy of ASC09 in the treatment of COVID-19. One current clinical trial is set to evaluate the efficiency and safety of ASC09/ritonavir and lopinavir/ritonavir for COVID-19 infections[44]. The study is a randomized, open-label trial and is estimated to have 160 participants[44]. Further clinical trials are needed to determine whether ASC09 is an efficacious therapeutic option.

Azvudine

Chemical composition: Azvudine, also known as FNC, is a cytidine analogue. It is a substrate for deoxycytidine kinase and is phosphorylated to deoxycytidine[45]. Azvudine is used in the treatment of HIV-1 infected patients and has been introduced in large part due to the emergence of resistance against previously created nucleoside analogues, namely 3TC[45].

Mechanism of action: Azvudine is a nucleoside reverse transcriptase inhibitor (NRTI) that has activity against HIV-1, HIV-2, hepatitis B, and hepatitis C[45]. The drug is activated after phosphorylation into an NRTI-triphosphate derivative[45]. As an NRTI-triphosphate derivative, the drug competes with deoxynucleoside triphosphates for incorporation into the viral strand by the enzyme reverse transcriptase[45]. The NRTI derivative lacks a 3'-OH group, so the incorporation into the viral strand prevents elongation[45].

Pharmacokinetics: Azvudine is currently being tested in clinical trials for HIV treatment and COVID-19; therefore, there is currently no published information about the pharmacokinetics of Azvudine. Regarding HIV, computer modeling has been used to predict the binding of Azvudine to reverse transcriptase[45].

Adverse effects: There is currently no clinical trial data available describing the adverse effects of Azvudine in the treatment of COVID-19.

Dosage: Dosage information for Azvudine as a treatment for COVID-19 is not currently available.

Randomized clinical trials: To date, there are no completed clinical trials evaluating the efficacy of Azvudine in the treatment of COVID-19. One clinical trial is studying the efficacy of Azvudine in the treatment of COVID-19-related pneumonia[46]. The study is a randomized, double blinded, double dummy, parallel controlled study[46]. Further clinical trials are needed to determine whether Azvudine is an efficacious therapeutic option.

Favilavir/Favipiravir/T-705/Avigan

Chemical composition: Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a pyrazine-carboxamide derivative and a pyrazine analogue that was initially approved for use against influenza[47]. Its activity is primarily against RNA viruses. It has known activity against influenza and has been promising in the treatment of avian influenza. It has been studied for the treatment of Ebola virus, Lassa virus, and COVID-19[47].

Mechanism of action: Favipiravir is converted to its active form, favipiravir-ribofuranosyl-5'-triphosphate, which then inhibits viral RNA-dependent RNA polymerase. Inhibition of the viral polymerase halts transcription and replication of

the viral genome[47]. It is thought that it is incorporated into an RNA strand, preventing elongation and proliferation of the viral genome[48]. Favipiravir is also reported to prevent the entry and exit of the virus in host cells[49].

Pharmacokinetics: Favipiravir is reported to have a bioavailability of 97.6%[50]. Its volume of distribution is approximately 15-20 L, and 54% of the drug appears to be plasma protein bound with 65% of this fraction being bound to albumin and 6.5% bound to a1-acid glycoprotein[50]. The drug is predominantly excreted renally, and its elimination half-life is reported to be between 2 to 5.5 h[50].

Adverse effects: The safety profile of Favipiravir in the treatment of COVID-19 is yet to be established. It is known to cause QT prolongation[50]. Additionally, it is recommended that cardiac and hepatic monitoring take place during treatment[50]. Favipiravir is a known teratogen and should be avoided in women who may become or are confirmed to be pregnant[48].

Dosage: Currently, the safety and efficacy of Favipiravir for the treatment of COVID-19 is being evaluated in a number of clinical trials. As such, there is not currently a proven recommended dosage. Open-label studies in China have used 1600 mg twice daily on the first day of treatment and 600 mg twice daily used for the following 7-10 or 14 d, respectively[33,51,52]. There is a need for continued clinical trials to determine an efficacious dose.

Randomized clinical trials: Limited clinical trial data regarding the efficacy of Favipiravir for COVID-19 infections is available. A small, open label, prospective, randomized multicenter study in China evaluated the use of Favipiravir *vs* Arbidol for patients with COVID-19[33]. It was found that the use of Favipiravir was associated with a greater degree of clinical recovery, defined as greater than 72 h of temperature less than 36.6 degrees C, respiratory rate less than 24/min, oxygen saturation greater than 98% on room air, and either mild or no cough when compared to Arbidol[33]. Clinical recovery rates were greater in both moderate (71% *vs* 56%) and severe cases of COVID-19 (6% *vs* 0%)[33]. In an additional open-label, nonrandomized trial of patients in China with non-severe COVID-19 infection, it was found that the use of Favipiravir was associated with decreased median time to viral clearance when compared to a control group receiving lopinavir/ritonavir treatment (4 d *vs* 11 d)[52]. The patients also noted improvements on chest CT scan on day 14[52]. Additional clinical trials are currently underway[53-55].

Xofluvaa (Baloxavir marboxil)

Structure/mechanism of action: Baloxavir marboxil is a cap-dependent endonuclease protein inhibitor that acts on influenza A and B viruses[56,57]. This inhibits mRNA synthesis, thus blocking viral replication[56,57]. It is currently FDA approved for the treatment of acute uncomplicated influenza A and B infections in individuals aged 12 and older who have been symptomatic for no more than 48 h.

Pharmacokinetics: Baloxavir marboxil is metabolized to an active form, Baloxavir acid[56]. The median time to peak plasma concentration is 4 h, and the mean half-life is 79.1 h[56]. It is 93 to 94% protein bound, and is primarily excreted in the feces (80%) with smaller amounts being excreted renally (15%)[56]. It is metabolized by the UGT1A3 and CYP3A4 pathways[56].

Adverse effects: Currently, only one randomized clinical trial has assessed the use of Baloxavir marboxil in the treatment of COVID-19. Because of this, there is limited data available regarding side effects of Baloxavir marboxil in COVID-19 patients. In studies evaluating the drug for the treatment of patients with influenza, the most common adverse effects were diarrhea (3.2%), bronchitis (2.6%), nasopharyngitis (1.5%), nausea (1.5%), and sinusitis (1.1%), although it was thought that these adverse events were not likely due to the trial regimen[58].

Dosage: The dosing protocol used in one of the only documented randomized control trials was 80 mg of Baloxavir marboxil once daily on day 1 and day 4[59]. Additionally, if patients still test positive for COVID-19 on day 7, an additional 80 mg dose can be given[59]. The total amount of doses given is not to exceed three 80 mg doses[59].

Randomized clinical trials: Randomized clinical trial data for the use of Baloxavir marboxil in COVID-19 is limited. One exploratory, single center, open-label, randomized control trial in China compared the addition of Baloxavir marboxil to

Favipiravir and control along with the current standard antiviral treatment regimen in patients with confirmed COVID-19 infection[59]. The current standard regimen included either Lopinavir/Ritonavir in combination with inhaled interferon-alpha or Darunavir/Cobicistat and Arbidol in combination with inhaled interferon alpha[59]. 29 patients were included in the study, and they were assigned to either receive Baloxavir marboxil, Favipiravir, or control, in addition to standard antiviral therapy. Twenty-four patients in the trial tested negative for COVID-19 within 14 d of starting the trial. The percentage of patients turning virus negative was 70%, 77%, and 100% in the Baloxavir group, Favipiravir group, and control group respectively[59]. Additionally, the daily viral load of the patients in each group was measured throughout the course of the trial, and the addition of Baloxavir or Favipiravir did not appear to improve the time to achieve half viral clearance when compared to control[59]. Based on this study, there is no evidence that Baloxavir marboxil is an effective treatment against COVID-19 patients. Additional studies may be necessary to confirm these findings.

Remdesivir

Chemical composition: Remdesivir (GS-5734) is a phosphoramidate prodrug of a 1'-cyano-substituted nucleotide analogue[60]. Its triphosphate form (RDV-TP) resembles adenosine triphosphate (ATP) and is used as a substrate of several viral RNA-dependent RNA polymerase enzymes or complexes. It is a broad-spectrum antiviral medication, with activity against RNA viruses such as Ebola, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus (RSV), Nipah virus (NiV), and Hendra virus. It has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses[61-63].

Mechanism of action: Replication of SARS-CoV-2 depends on the viral RNA-dependent RNA polymerase, which is the target of the nucleotide analogue Remdesivir. The SARS-CoV-2 RNA-dependent RNA polymerase is composed of the non-structural proteins nsp8 and nsp12[64]. Enzyme kinetics indicated that this RNA-dependent RNA polymerase efficiently incorporates the active triphosphate form of Remdesivir into RNA[64]. Additionally, the mechanism of Remdesivir's anti-MERS-CoV activity is likely through premature termination of viral RNA transcription as shown in biochemical assays using recombinant EBOV, NiV, and RSV polymerase[64]. This drug has shown potent inhibitory activity against Remdesivir with intact proof reading and with low level of resistance to target mutations[64].

Pharmacokinetics: Remdesivir has a short plasma half-life of 0.39 h[65]. When given to cynomolgus monkeys, a 10 mg/kg dose rapidly distributed to the testes, epididymis, eyes, and brain within 4 h[65]. Levels measured in the brain were much lower than other tissues due to poor blood-brain barrier penetration, however levels in the brain were detectable at 168 h after the dose was given. It is primarily eliminated renally (74%), with a smaller amount of fecal excretion (18%)[66].

Adverse effects: During a study by Grein *et al*[67], the most common adverse events noted during use of Remdesivir in patients with COVID-19 included rash, diarrhea, hypotension, abnormal liver function and renal impairment. Serious adverse events such as acute kidney injury, septic shock, and multi-organ failure were noted in 23% of patients[67]. During the study, 60% of participants suffered at least one adverse event and 8% discontinued treatment prematurely[67].

Dosage: Current dosage recommendation of Remdesivir in COVID-19 is a bolus dose of 200 mg IV diluted in normal saline (0.9%) or 5% dextrose to be given over 60 min on day 1, followed by 100 mg IV to be given diluted over 60 min for the next 9 d[66].

Randomized clinical trials: Wang *et al*[68] enrolled and randomly assigned 237 patients to a treatment group (158 to Remdesivir and 79 to placebo). Remdesivir use was not associated with a difference in time to clinical improvement [hazard ratio 1.23 (95%CI 0.87–1.75)][68]. Although not statistically significant, patients receiving Remdesivir had a faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 d or less [hazard ratio 1.52 (0.95-2.43)][68]. Adverse events were reported in 102 (66%) of 155 Remdesivir recipients *vs* 50 (64%) of 78 placebo recipients[68]. Remdesivir was stopped early because of adverse events in 18 (12%) patients *vs* four (5%) patients who stopped placebo early[68].

On April 29, 2020, the National Institute of Allergy and Infectious Diseases (NIAID) announced interim results of a randomized controlled trial named ACTT (Adaptive COVID-19 Treatment Trial) involving 1063 patients conducted at 68 sites (47 in United

States and 21 in Europe and Asia)[69]. Preliminary results indicate that the median time to recovery was 11 d for patients treated with Remdesivir compared to 15 d for those who received placebo, thereby suggesting that patients who received Remdesivir had a 31% faster time to recovery than those receiving placebo ($P < 0.001$)[69]. However, the survival benefit with Remdesivir was not statistically significant compared to the control, as the Remdesivir group had a mortality rate of 8.0% compared to 11.6% for the placebo group ($P = 0.059$)[69].

The SIMPLE trial is an open-label, randomized, phase 3 clinical trial comparing the clinical improvement of 5-d (short-course) *vs* 10-d (long-course) treatment duration of Remdesivir ($n = 397$) in hospitalized patients with severe (evidence of pneumonia and reduced oxygen levels, not requiring mechanical ventilation) COVID-19, in addition to the standard of care in 15 countries[70]. Secondary objectives included rates of adverse events and additional measures of clinical response in both treatment groups. The study showed that the 10-d course had similar outcomes compared to the 5-d course [odds ratio (OR) 0.75, 95%CI 0.51-1.12] assessed on day 14, without any new safety signals[70]. An exploratory analysis of this study suggested a larger benefit if Remdesivir was initiated within 10 d of symptom onset[70]. Pooled data from both study arms found that at day 14, 62% *vs* 49% of participants were discharged from the hospital, if Remdesivir was started within 10 d *vs* after 10 d of symptoms, respectively[70].

Beigel *et al*[71] conducted a double-blind, randomized, placebo-controlled trial using IV Remdesivir in adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either Remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 d[71]. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes[71]. Preliminary results from the 1059 patients (538 assigned to Remdesivir and 521 to placebo) indicated that those who received Remdesivir had a median recovery time of 11 d (95%CI, 9.0 to 12.0) as compared with 15 d (95%CI, 13.0 to 19.0) in those who received placebo (rate ratio for recovery, 1.32; 95%CI, 1.12 to 1.55; $P < 0.001$)[71]. The Kaplan-Meier estimates of mortality by 14 d were 7.1% with Remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95%CI, 0.47 to 1.04)[71]. Serious adverse events were reported for 21.1% in the Remdesivir group and 27% in the placebo group. Thus, Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of lower respiratory tract infection[71].

CELL AND RNA-BASED THERAPIES

Mesenchymal stem cells

Structural composition: Mesenchymal stem cells (MSCs) are considered to be a highly proliferative, minimally invasive, potential treatment of COVID-19[72]. MSCs are stem cells that are isolated from various body tissues, including dental pulp, menstruation blood, bone marrow, adipose tissues, buccal fat pad, and the fetal liver[72]. MSCs are multipotent stem cells and can be expanded easily to a clinical volume[73]. Clinical trials have not shown adverse reactions to allogeneic MSCs[73].

Mechanism of action: It is believed that COVID-19 triggers immune system over-activation that is responsible for damaging infected tissue. The immune system produces large amounts of pro-inflammatory factors, inducing a cytokine storm that may induce the overproduction of immune cells[74]. It is thought that MSCs prevent the cytokine storm by preventing the release of cytokines by the immune system and promoting repair through the reparative properties of stem cells[72]. Once the MSCs are given through an intravenous injection, the MSC population is trapped in the lung, which may help in the recovery of the lung's microenvironment, protect alveolar epithelial cells, cure lung dysfunction, and intercept pulmonary fibrosis in COVID-19-related pneumonia[75].

Adverse effects: There is currently no clinical trial data available describing the adverse effects of MSCs in the treatment of COVID-19.

Dosage: Dosage information for MSCs as a treatment for COVID-19 is not currently available.

Randomized clinical trials: Several clinical trials have been registered to investigate

the use of MSCs in the treatment of COVID-19. One study by Leng *et al*[75] evaluated the effects of MSC transplantation in 7 patients with COVID-19 pneumonia. At 48 h post MSC transplant, all 7 patients showed improvement of clinical symptoms[75]. MSCs have shown promise in the treatment of ARDS, inflammation, pneumonia, and sepsis, all of which contribute significantly to mortality in COVID-19 patients[76]. The safety and efficacy of intravenous MSC therapy has not been shown, and there is some concern about this mode of delivery because of the high levels of procoagulant tissue factor present in MSC infusions[76]. This could of course be dangerous for patients with COVID-19, who are already thought to be in a hypercoagulable state[76].

MultiStem

Structural composition: MultiStem is an allogeneic cell therapy made of multipotent adherent bone marrow cells[77]. MultiStem cells have been studied for the treatment of ischemic stroke, ulcerative colitis, acute myocardial infarction, and graft *vs* host disease prophylaxis in allogenic hematopoietic stem cell transplant[78].

Mechanism of action: MultiStem cells appear to be therapeutic due in part to their pro-angiogenic effects and their ability to modulate the immune system[79]. MultiStem cells lack major histocompatibility complex (MHC) II, which means that they do not create a proliferative response when cultured alongside allogeneic T-cells and ultimately that they reduce T cell proliferation when the T cells are stimulated with irradiated, allogeneic stimulator cells[80]. MultiStem is also immunosuppressive due to the presence of soluble factors[78].

Adverse effects: There is currently no clinical trial data available describing the adverse effects of MultiStem in the treatment of COVID-19. One study looked at the administration of MultiStem alongside hematopoietic stem cell transplants[81]. They found that overall, there was good tolerance to the therapy with no associated infusion toxicity, increased infection incidence, or graft failure[81].

Dosage: There is currently no clinical trial data available describing the appropriate dosage for MultiStem in the treatment of COVID-19.

Randomized clinical trials: There is currently no clinical trial data available describing the efficacy and safety of MultiStem in the treatment of COVID-19. One clinical trial is hoping to look at the efficacy of MultiStem in the treatment of COVID-19 induced ARDS. The study is a multicenter, open-label, single active treatment arm study followed by a double-blind, randomized, placebo-controlled phase. The goals of this study are to evaluate the safety and efficacy of MultiStem for people with moderate to severe ARDS[82].

RNA based therapies

Structural composition: Small interfering RNAs, also known as short interfering RNAs, silencing RNAs, or siRNAs, are non-coding, double stranded RNA molecules that are typically 20-25 base pairs in length.

Mechanism of action: SiRNA molecules are capable of regulating gene expression through RNA interference[83]. RNA interference allows for post-transcriptional gene silencing and degradation of target mRNAs[84]. SARS-CoV-2 has a protease sequence (specifically in protease 3CL) known as nsp5 that appears to be highly conserved, making this sequence a potential target of siRNA therapeutics[85]. Other targets that have been considered are the viral helicase and the viral RNA-dependent RNA polymerase[85]. It is believed that siRNAs can target these highly conserved sequences of SARS-CoV-2 and suppress the viral impact in the lungs, ultimately allowing for treatment of COVID-19 infection[86].

Pharmacokinetics: Information regarding the pharmacokinetics of RNA based therapy in the treatment for COVID-19 is not currently available.

Adverse effects: There is currently no clinical trial data available describing the adverse effects of RNA based therapy in the treatment of COVID-19. Previous work has shown that though beneficial, siRNA can induce unwanted side effects[85]. The side effects associated with siRNA therapy may be due to a phenomenon called off-targeting, which is when siRNAs interfere with transcripts besides the target RNA[87]. The first evidence of this effect was reported in 2003 by Jackson *et al*[89] Strategies have been proposed to minimize off-targeting, most of which deal with planning siRNA experiments and designing appropriate siRNA for therapeutics[87].

Dosage: Dosing information for RNA based therapies as a treatment for COVID-19 is not currently available.

Randomized clinical trials: To date, there are no published clinical trials evaluating the efficacy of RNA based therapy in the treatment of COVID-19. Researchers have previously tested the efficacy of *in vitro* utilization of amidoamine nanocarriers for siRNA onto lung epithelial cells, which may be useful in targeting SARS-COV-2 because the primary site of infection is the ciliated cells of the human lung[86,89].

MISCELLANEOUS TREATMENT

APN01: recombinant human angiotensin-converting enzyme

Structural composition: APN01 is a soluble, glycosylated recombinant form of the human angiotensin-converting enzyme 2 (rhACE2). It has both antihypertensive and antineoplastic properties[90].

Mechanism of action: The drug is thought to cleave angiotensin II to form angiotensin-1-7. Angiotensin-1-7 is thought to have a variety of functions, including counteracting the cardiovascular actions of angiotensin II and inhibiting cyclooxygenase-2. It is believed that when pro-inflammatory prostaglandins are made, the angiotensin-1-7 G-protein-coupled receptor Mas is activated, potentially diminishing tumor cell proliferation[90]. Previous research showed that ACE2 is a key receptor for SARS-CoV-2, and that APN01 could block early stages of SARS-CoV-2 infections, suggesting that treatment with APN01 may be useful in the treatment of COVID-19[91]. One publication showed that SARS-COV-2 replicates in human blood vessels and kidneys, and this replication may be blocked by APN01[91]. By binding to the spike protein, rhACE2 can reduce binding to ACE2 at the cell membrane, leading to decreased internalization of SARS-COV-2 and reduced viral load[91].

Pharmacokinetics: Information regarding the pharmacokinetics of APN01 in the treatment for COVID-19 is not currently available.

Adverse effects: Information regarding the adverse effects of APN01 in the treatment for COVID-19 is currently not available.

Dosage: Dosage information for APN01 as a treatment for COVID-19 is not currently available.

Randomized clinical trials: APN01 is currently in clinical trials for its efficacy in treating COVID-19. One study aims to enroll 200 participants in a randomized, double-blinded study[92]. In vitro and *in vivo* studies are needed to truly understand the effects of APN01 in COVID-19 infections.

CQ/HCQ

Structural composition: CQ and HCQ belong to a class of drugs known as 4-Aminoquinolines[93]. Both have a flat aromatic core and are weakly basic[94]. CQ has been historically used as an antimalarial and anti-amoebic agent, while HCQ has been used as an antirheumatic agent, as well as more recently as a therapy for the Zika virus and the 2004 SARS outbreaks[95]. HCQ is a more tolerable and safer derivative of CQ and has potent activity against SARS CoV-2 *in vitro*[96]. HCQ differs from CQ due to the presence an N-Hydroxyethyl side chain in place of the N-diethyl group, which makes it more soluble[95].

Mechanism of action: Numerous mechanisms have been postulated as to how CQ/HCQ achieves its anti-malarial, ani-viral, and anti-rheumatic effects, however the overall picture remains poorly understood. The most common theory is that as they are both weak bases, they tend to accumulate in lysosomes, increasing the pH and disrupting several enzymes that ultimately leads to the inhibition of the post-translational modification of newly synthesized proteins[97]. This disruption of the protein degradation pathway interferes with antigen processing and can prevent MHC class II mediated antigen presentation resulting in its anti-rheumatic effects[97]. Another theory is that they may interfere with endosome mediated viral entry secondary to alkalization of the entry endosomes[97]. This change in endosomal pH also allows CQ/HCQ to downregulate toll-like receptors (TLRs) along with TLR-mediated signal transduction[95]. They also are known to decrease the production of cytokines such as

IL-1, IL-6, and tumor necrosis factor by mononuclear cells[98].

Pharmacokinetics: CQ/HCQ are absorbed in the upper gastrointestinal tract with the fraction absorbed being approximately 74%[93]. They are approximately 50% plasma protein bound, with an extremely long half-life (> 40 d)[93,99]. It is believed that the extended half-life is likely due to a large volume of distribution[93]. They are primarily metabolized by the liver, specifically the CYP3A4 and CYP2C3 enzymes, and are renally cleared[93]. CQ/HCQ bind strongly to melanin, and can deposit in high concentrations in the eyes and skin[100].

Adverse effects: CQ/HCQ are both well tolerated medications. The most common side effects include gastrointestinal effects such as nausea, vomiting, dyspepsia and cramps[101]. It may also cause headaches, tinnitus, itching, and rashes[102]. The dose limiting side effect is macular retinopathy, however this is more common in CQ as opposed to HCQ[103] Both medications have QT prolongation effects which may lead to cardiac arrest, especially when combined with Azithromycin, which has been done for the treatment of COVID-19[104].

Dosage: HCQ dosage consists of 6 d of therapy, with a 400 mg dose given every 12 h for the first day, and 200 mg given every 12 h for the subsequent 5 d[105]. HCQ was given emergency use authorization by the FDA in March 2020, however, was subsequently revoked in June 2020 due to safety concerns. It is currently not recommended unless a patient is enrolled in a clinical trial[106].

Randomized clinical trials: HCQ had been implemented in the treatment of COVID-19 prior to any meaningful randomized clinical trials. This was done on the basis of *in vitro* data as well as an open label non-randomized clinical trial published in March 2020 by Gautret *et al*[105]. This trial had enrolled 20 patients to receive HCQ 200 mg three times a day for a total of 10 d[105]. The control group (16 patients) were patients who had refused treatment or had contraindications to HCQ. The primary endpoint was virologic clearance at day 6 post-inclusion. Results showed that at day 6 post-inclusion, 70% of patients receiving HCQ had achieved virologic clearance as compared to 12.5% in the control group[105]. The limitations of this study include small sample size as well as lack of randomization and blinding.

The first true randomized control trial to evaluate efficacy of HCQ for treatment COVID-19 was conducted by Tang *et al*[107] This was a multi-center, open label, randomized control trial comparing viral clearance at 28 d in 150 patients, randomized to a HCQ arm and a standard of care arm with intention to treat analysis. Patients who had received HCQ received a dose of 600 mg twice daily for three days followed by 400 mg twice daily for 2-3 wk[107]. The results showed no discernable difference in viral clearance between the HCQ group and standard of care group (85.4% and 81.3% respectively)[107].

A randomized control trial to assess safety and efficacy of higher doses of CQ was conducted by Borba *et al*[108] in March 2020. This was a parallel, double masked, randomized clinical trial involving 81 patients. The participants were divided into two groups, with 41 patients receiving high dose CQ and 40 receiving low dose CQ. High dose CQ was considered 600 mg twice daily for 10 d while low dose was considered 450 mg twice daily for the first day and then once daily for the subsequent 4 d[108]. Primary outcome was a decrease in mortality by 50% in the high dose group as opposed to the low dose group[108]. Results demonstrated a higher mortality at day 13 in the high dose group compared to the low dose group (39% and 15% respectively)[108]. Due to safety concerns secondary to increased adverse effects in the high dose group the trial was discontinued prematurely[108].

The RECOVERY trial was a UK-based randomized clinical trial to test numerous drugs for COVID-19, including HCQ[109]. A total of 1542 patients were randomized to HCQ as compared with 3132 randomized to standard of care alone. The primary endpoint was 28-d mortality, which showed no significant difference between the two groups (25.7% HCQ *vs* 23.5% standard care) [95%CI 0.98-1.26; $P = 0.1$][109]. On June 5th 2020, the chief investigators of the study had released the afore-mentioned preliminary results as well as a statement conveying the lack of any meaningful mortality benefits in patients with COVID-19 and that the investigators have stopped enrolling participants in the HCQ arm of the RECOVERY trial[109]. The results of the HCQ arm of RECOVERY trial have not been published.

HCQ has also been evaluated as a possible post-exposure prophylaxis agent for COVID-19. This was done in the context of a randomized, double-blinded, placebo-controlled trial[110]. The study population included adults who had high-risk household

or occupational exposure (distance less than 6 ft for more than 10 min without a mask) or moderate risk (the same distance with a face mask but no eye shield) to someone with laboratory confirmed COVID-19[110]. Within 4 d of exposure, patients were randomly assigned to receive either placebo or HCQ. The primary outcome was the incidence of laboratory-confirmed COVID-19 or illness compatible with COVID-19 within 14 d[110]. There were 821 asymptomatic participants, and incidence of COVID-19 in the high-risk exposure population did not differ significantly[110].

Azithromycin

Structural Composition: Azithromycin is an azalide which is a subclass of macrolide antibiotics derived from the prototype Erythromycin[111]. Azithromycin has a nitrogen added to the 14-membered ring of erythromycin, creating a new 15 membered compound[111]. The addition of nitrogen creates a dibasic molecule which results in improved antimicrobial activities, pharmacokinetics and fewer side effects as compared with Erythromycin[112].

Mechanism of action: Azithromycin is a bacteriostatic antibiotic which prevents bacterial growth *via* inhibition of bacterial protein synthesis by binding to the 50 s ribosomal subunit[111]. Due to its dibasic nature Azithromycin is taken up by white blood cells (WBC) and fibroblasts resulting in a neutrophilic intracellular:extracellular ratio of 226:1 after 24 h of incubation[113]. This WBC uptake is believed to be the reason for Azithromycin's effective intracellular and extracellular activity, as well as increased drug levels localized to the site of infection[113]. Regarding the mechanism of action against SARS-CoV-2, one in-vitro study suggested that due to its intracellular accumulation, Azithromycin increases the pH of intracellular organelles[114]. This alteration in pH would interfere with intracellular viral activities, a mechanism very similar to CQ/HCQ[114]. Another potential mechanism of action is the anti-inflammatory activity shown by macrolides, thus alleviating the proinflammatory state of COVID-19[106].

Pharmacokinetics: Azithromycin is rapidly absorbed after oral dosing, with excellent tissue penetration and a long half-life of roughly 68 h[115]. It has a large volume of distribution of approximately 31 L/kg. The primary route of elimination is *via* biliary excretion[116]. Approximately 6% of azithromycin is excreted unchanged in urine[116].

Adverse effects: Azithromycin is generally safe and well tolerated. The most commonly reported side effects are gastrointestinal and include nausea, diarrhea and abdominal pain[117]. Rash, transaminitis, and hepatomegaly have also been seen with azithromycin[117]. Rarely it may cause QT interval prolongation and should be used with caution when administering to patients concomitantly with other QT-prolonging drugs such as CQ/HCQ[117].

Dosage: Since the outbreak of COVID-19, many clinicians are using Azithromycin off-label, usually concomitantly with HCQ. Due to lack of supporting evidence regarding its efficacy, it is no longer used in the treatment of COVID-19. It was given as a 500 mg dose on day 1, followed by 250 mg for the next four days for a total of a 5-d treatment course[105]. Currently it is only recommended that Azithromycin be administered in the context of clinical trials[106].

Randomized clinical trials: All clinical trials conducted utilizing Azithromycin for the treatment of COVID-19 have been performed in the context of Azithromycin being administered as an adjunct to CQ/HCQ. The are no well-controlled, prospective, randomized clinical trials evaluating the efficacy of azithromycin for the treatment of COVID-19.

Colchicine

Structural composition: Colchicine is a tricyclic, lipid soluble alkaloid. Its chemical formula is N-(5,6,7,9, tetrahydro-1,2,3,10, tetramethoxy-9 oxobenzo[a] hep-tain-7-yl) acetamide. Colchicine has long been used for the treatment of gout, but has since been known to be used in the treatment of several disorders including familial Mediterranean fever, primary biliary cirrhosis, psoriasis, sarcoidosis, scleroderma, amyloidosis, pericarditis, Sweet syndrome, and Behcet's disease[118].

Mechanism of action: There are several proposed mechanisms regarding the potential efficacy of Colchicine as a therapeutic for COVID-19. First, Colchicine is believed to exert its anti-inflammatory effects through binding to beta-tubulin in neutrophils[119]. This allows for the inhibition of assembly and polymerization of microtubules,

interfering with several cellular functions. This includes production of chemokines and decreasing neutrophil degranulation, chemotaxis, and phagocytosis[119]. Additionally, Colchicine has been shown to be an inhibitor of the NLRP3 inflammasome, which plays a major role in the pathophysiology of ARDS[120]. Several SARS-CoV-2 proteins have been hypothesized to activate the NLP3 inflammasome, thus leading to the development of ARDS[120]. Inactivation of the neutrophilic function and inhibition of the NLP3 inflammasome lead to the anti-inflammatory and cytokine suppression effects that may contribute to Colchicine's potential mechanism against COVID-19.

Pharmacokinetics: After administration, Colchicine is absorbed in the jejunum and ileum[121]. The peak plasma concentration after oral administration occurs between roughly 30 and 90 min [119,121]. The half-life is thought to be between 9.3 and 10.6 h, and bioavailability has been shown to range from 24% to 88%[119,122]. Colchicine is thought to be widely taken up by tissues, and its protein binding is between 10% and 31%[119,121]. It is thought to be metabolized by the cytochrome P450 CYP3A4 (20%) and it is excreted primarily *via* the feces[118,119]. It is also thought that 10%-20% of the available metabolites are excreted *via* the urine[118].

Adverse effects: There is currently no clinical trial data available describing the adverse effects of colchicine in the treatment of COVID-19. Colchicine is thought to be generally safe and well tolerated, although the therapeutic window is narrow[118]. Current data suggests that side effects of Colchicine in non COVID-19 use includes GI side effects such as vomiting, diarrhea, cramping, and abdominal pain[118,119]. Additionally, leukopenia and neuromuscular complications are rare side effects that have been reported[118].

Dosage: Dosage information for Colchicine as a treatment for COVID 19 is not currently available.

Randomized clinical trials: To date, there are no published clinical trials evaluating the efficacy of Colchicine in the treatment of COVID-19. A retrospective study by Gendelman *et al*[123] examined the protective role of Colchicine against COVID-19 by determining the rate of baseline usage of the drug in patients with RT-PCR confirmed COVID-19 infection and those who tested negative. The total sample included 14520 subjects, of which 1317 tested positive. There was no significant difference found in Colchicine usage between those who tested positive (0.53%) and those who tested negative (0.48%)[123]. This retrospective study did not suggest a protective effect of Colchicine against COVID-19. Further clinical trials are needed to determine whether Colchicine is an efficacious therapeutic option.

Corticosteroids/methylprednisolone

Structural composition: Methylprednisolone is a glucocorticoid that is a prednisolone derivative. It is more potent than prednisone[124]. Methylprednisolone exists in both a succinate formulation (Solu-Medrol), and an acetate suspension (Depo-Medrol).

Mechanism of action: It is speculated that the anti-inflammatory and antifibrotic properties of corticosteroids may prevent an extensive cytokine response, which would result in a faster resolution of pneumonia and systemic inflammation[125,126]. Methylprednisolone is a corticosteroid; therefore, it binds to the glucocorticoid receptor and inhibits proinflammatory signals and promotes anti-inflammatory signals[127]. The binding of the drug to the glucocorticoid receptor alters gene expression, leading to downstream effects over the course of hours to days[127]. These effects may be anti-inflammatory when administered at lower doses, or immunosuppressive when administered at higher doses[127].

Pharmacokinetics: The bioavailability of oral methylprednisolone acetate is 89.9%, and the average volume of distribution is approximately 1.38 L/kg[128,129]. It is 76.8% protein bound in plasma[129]. It is thought that the drug is metabolized mostly by 20-ketosteroid reductases and 11beta-hydroxysteroid dehydrogenases[129]. The half-life is 2.3 h[128,129]. Its clearance rate is 336mL/h/kg on average[129]. One study in animals showed 25-31% of the drug was eliminated in urine while 44-52% was eliminated *via* fecal route[130].

Adverse effects: Information regarding adverse events related specifically to COVID-19 infections is not available. One study of methylprednisolone use in Kawasaki disease showed that adverse effects included sinus bradycardia, hyperglycemia, and hypertension[131]. Hypothalamic-pituitary-adrenal (HPA) suppression is also possible

with methylprednisolone administration[132].

Dosage: One retrospective study used 1-2 mg per kg daily IV for 5-7 d[133]. A randomized control study administered 40 mg IV every 12 h for 5 d[134].

Randomized clinical trials: One multicenter, open label randomized controlled study completed in China compared the use of methylprednisolone paired with standard care in patients that had progressed to acute respiratory failure. The results of this study have not yet been published[134]. Additional studies regarding the efficacy of methylprednisolone have been completed. One retrospective, observational single-center study collected data from 201 confirmed COVID-19 infected patients who had pneumonia that progressed to ARDS[135]. In these patients, methylprednisolone appeared to reduce the risk of death[135]. In another retrospective, observational single-center study, data was collected from 46 patients who had severe, confirmed COVID-19 pneumonia that progressed to acute respiratory failure. The study found that methylprednisolone use was associated with shortened disease and improved clinical symptoms (including fever and hypoxia)[133].

As part of the RECOVERY trial, dexamethasone has been evaluated as a potential treatment for COVID-19[137]. This was a controlled, open-label, adaptive trial in which a total of 2114 patients were allocated to receive Dexamethasone (6 mg once daily for up to 10 d) and 4321 were allocated to usual standard of care[136]. The primary outcome was all-cause mortality at 28-d post randomization[136]. Preliminary results showed a decrease in mortality in the Dexamethasone arm as opposed to the standard of care arm (22.9% *vs* 25.7% mortality respectively)[136]. It was also noted that there were variations in the proportional and absolute mortality rate reductions based on the level of ventilatory support that patients initially required[136]. Dexamethasone decreased mortality by one-third in patients receiving mechanical ventilation (29.3% *vs* 41.4% mortality) and by one-fifth in those who were receiving non-invasive oxygenation (23.3% *vs* 26.2% mortality)[136].

Ivermectin

Structural composition: Ivermectin is a semisynthetic derivative of avermectin B1, consisting of an 90:10 mixture of 22,23-dihydro-avermectin B1a and 22,23-dihydro-avermectin B1b[137,138]. Avermectins are a group a pentacyclic sixteen-membered lactones derived from the soil bacterium Streptomyces avermitilis[139]. It is a broad spectrum antiparasitic, however it has shown antiviral activity against a number of pathogens including dengue virus, yellow fever virus, and HIV1 virus, among others[140-142].

Mechanism of action: Although the potential mechanism of action of Ivermectin against SARS-CoV-2 is unknown, the novel coronavirus SARS-CoV-2 is very similar to the better studied SARS-CoV. They are both single-stranded positive sense RNA viruses, and SARS-CoV is thought to utilize IMPalpha/B1, a heterodimer responsible for integrase protein nuclear import[143]. It is thought that Ivermectin may play a role in inhibiting viral nuclear import into the host cell through its interactions with IMPalpha/B1[143].

Pharmacokinetics: Ivermectin is only approved for oral administration in humans. Following oral administration, plasma concentrations are similar to the dose received[138]. It is widely distributed in the human body, bound strongly to plasma proteins at 93.2%[137]. After administration, the compound has been found to be present in adipose tissue, skin, fascia, and nodule[137]. It is found at highest concentrations in adipose tissue[137]. The drug is metabolized by the cytochrome P450 system, and is excreted almost exclusively in feces over a 12 d period, with only 1% of the dose given being excreted in the urine[137,138].

Adverse effects: The adverse effects of Ivermectin as a therapy for COVID-19 are unknown, however it is thought to be very well tolerated in the treatment of parasitic infections. Side effects noted from clinical trials include fatigue (0.9%), abdominal pain (0.9%), anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), dizziness (2.8%), vertigo (0.9%), tremor (0.9%) and Mazzotti reaction, including arthralgias, lymph node enlargement and tenderness, edema, and urticarial rash[138].

Dosage: No human trials have been published regarding the usage of Ivermectin as a treatment modality for COVID-19. For the treatment of strongyloidiasis, Ivermectin is given as a single oral dose providing 200 mcg per kilogram of body weight[138]. For Onchocerciasis, a single dose providing 150 mcg per kilogram of bodyweight is

given[138].

Randomized clinical trials: To date, there have been no studies published regarding the efficacy of Ivermectin as a potential treatment for COVID-19 in humans. However, Caly *et al*[143] tested the anti-viral effects of Ivermectin against COVID-19 infected Vero/hSLAM cells in vitro, and found that at 24 h, the amount of viral RNA was reduced by 93% in the infected cells. At 48 h, there was greater than 5000 fold decrease in the amount of viral RNA seen in COVID-19 infected cells[143]. There was no toxicity observed in any of the samples during the study[143]. While this is promising, clinical trials are needed to determine the safety and efficacy of Ivermectin as a potential treatment for COVID-19.

Convalescent plasma

Mechanism of action: Convalescent plasma is the collection of plasma from an individual who has previously been infected with COVID-19 and developed antibodies. Administration of the plasma from patients with resolved infections leads to passive immunization, and reception of these antibodies in those who are currently sick may lead to reduced symptom burden and mortality. The use of convalescent plasma during pandemics is not a new trend, as it was used during the SARS, MERS, Ebola, and H1N1 pandemics as well[144-147]. Theoretically, the use of convalescent plasma should be given to infected patients early in the course of illness before the immune system has had the time to develop antibodies on its own.

Adverse events: Adverse effects have varied. Li *et al*[148] reported adverse events in 2 of 52 patients receiving convalescent plasma, which included transfusion reactions such as febrile non-hemolytic and severe transfusion associated dyspnea. Shen *et al*[149] reported no adverse events in 5 critically ill patients receiving convalescent plasma. Finally, a study by Duan *et al*[150] found no serious adverse events in 10 ICU patients receiving plasma, however one patient did develop an evanescent facial red spot.

Dosage: Dosing of convalescent plasma for the treatment of COVID-19 has varied among the current available studies. Dosage of convalescent plasma given in a clinical trial by Li *et al*[148] was 4-13 mL/kg of recipient body weight, transfused at 10 mL for 15 min, followed by 100 mL per hour. Shen *et al*[149] gave 200-250 mL twice on the same day as collection from the donor. Lastly, Duan *et al*[150] gave patients one dose of 200 mL of convalescent plasma.

Randomized clinical trials: Li *et al*[148] performed an open-label, multicenter, randomized clinical trial at 7 hospitals in Wuhan, China. The trial enrolled 103 patients hospitalized with COVID-19. Fifty-two patients received convalescent plasma in addition to standard treatment (based on Chinese national treatment guidelines and hospital practice guidelines for COVID-19) and 51 patients received standard treatment alone[148]. Patients received plasma at a dose of 4-13 mL/kg of recipient body weight[148]. The primary outcome was time to clinical improvement within a 28 d period, defined as either discharge or a reduction of 2 points on a 6 point COVID-19 severity scale[148]. For all patients, the authors found no significant difference between the convalescent plasma group and control (51.9% *vs* 43.1%; $P = 0.26$)[148]. Furthermore, there was no significant difference in 28 d mortality between the two groups (15.7% *vs* 24.0%; $P = 0.30$)[148]. Adverse events were reported in two patients receiving convalescent plasma treatment, both of which were transfusion related reactions[148]. This trial did not demonstrate significant time to improvement in patients receiving convalescent plasma for the treatment of COVID-19.

Shen *et al*[149] describe a case series of 5 critically ill patients in Shenzhen, China with COVID-19 and ARDS receiving convalescent plasma in addition to antiviral agents. The patients received two transfusions of 200-250 mL of convalescent plasma in one day. In this trial, viral load declined and was negative in all five patients within 12 d of treatment[149]. Furthermore, all patients saw reductions in temperature within 3 d, improvements in chest imaging, and improvements in PaO2/FiO2 ratio. Four of five patients receiving mechanical ventilation no longer required respiratory support within 9 d of receiving convalescent plasma[149]. No adverse events were reported. Although this study was a small case series, and there were no controls, it shows promise for the use of convalescent plasma in the treatment of COVID-19.

Lastly, Duan *et al*[150] performed a pilot study including 10 patients with severe COVID-19. Patients received a single 200 mL dose of convalescent plasma in addition to various antiviral therapies and intravenous methylprednisolone. Within 3 d, all 10 patients had significant improvement in their symptoms including fever, cough,

shortness of breath, and chest pain[150]. Additionally, 2 of 3 patients receiving mechanical ventilation were weaned to high flow nasal cannula, and one patient was able to discontinue high flow nasal cannula[150]. All patients showed improvement of pulmonary lesions on CT after transfusion. Lastly, neutralizing antibody titers increased in 5 patients, and viral RNA decreased to undetectable levels in 3 patients after 2 d, three patients after 3 d, and one patient after 6 d[150]. This trial, again, was performed without controls. It does however show promise for the use of convalescent plasma in patients with severe COVID-19.

ECMO

ECMO is often used as a last resort in patients with critical pulmonary or cardiovascular compromise. ECMO has various configurations that can be altered based on the needs of the patient. The potential use of ECMO has been a hot topic in recent discussions. Positive ECMO experiences in critically ill patients infected with Middle Eastern respiratory syndrome (MERS) has encouraged some to use ECMO in those infected with COVID-19[151]. Theoretically, it is possible for ECMO to be used in COVID-19 infected patients to support cardiac and pulmonary function; however, the efficacy and validity in the clinical setting remains unanswered.

Mechanism of action: Most often, COVID-19 patients who may benefit from ECMO are those with ARDS refractory to standard treatment. Patients in this clinical stage have impaired gas exchange due to alveolar inflammation and edema. Therefore, patients require oxygenation assistance. There are several configurations of ECMO. Veno-venous ECMO (V-V ECMO drains blood from a large peripheral vein, oxygenates it *via* a synthetic lung and returns it to the circulation *via* a large peripheral vein. Newly oxygenated blood then flows through the normal circulatory pathways to provide oxygen to the rest of the body. V-V ECMO settings require that the patient's heart is functioning appropriately to ensure adequate blood distribution[152]. Suggested criteria for V-V ECMO use are PaO2/FiO2 < 100 mmHg, PCO2 > 60 mmHg, and/or arterial pH < 7.2[153].

When a patient's cardiovascular function is compromised, such as with COVID-19-induced myocarditis, veno-arterial ECMO (V-A ECMO) is the preferred ECMO configuration. In V-A ECMO, venous blood is drained, oxygenated *via* a synthetic lung and finally returned to the patient's circulatory system *via* a large peripheral artery that drains towards the aorta. The ECMO-induced increase in aortic blood flow improves peripheral perfusion[154]. V-V/V-A ECMO may be modified in difficult circumstances, such as those with superimposed sepsis or multi-organ dysfunction, in order to add extra lumen and convert the ECMO system from a double lumen to a triple lumen ECMO system. The additional lumen may help optimize settings per patient requirements[155].

Randomized clinical trials: To date, there are no published clinical trials evaluating the efficacy of ECMO in the treatment of COVID-19. ECMO has been used in patients who have been confirmed to have COVID-19 and in those suspected to have COVID-19 but whose status has not been confirmed. There has been some published work on the efficacy of ECMO despite the lack of clinical trials. One preliminary study form China showed a high mortality rate for COVID-related ARDS patients, reporting a mortality of 50% in a cohort of 28 patients[156]. A pooled analysis of the data from China, which included the data for 562 COVID-19 patients, studied the effects of ECMO and non-ECMO treatment in the 46% of patients who developed ARDS. Those who did not get treated with ECMO had a mortality rate of 70.9%, while those treated with ECMO had a mortality of 94.1%[157]. While some data exists that may speak to the efficacy and validity of using ECMO in those infected with COVID-19, there is still a need for randomized clinical trials to understand the effects of this therapy.

CONCLUSION

The COVID-19 pandemic has placed a tremendous burden on our healthcare systems, as well as on researchers and clinicians who are racing to find therapeutics that may be beneficial in combatting this morbid disease. Currently, there is no single treatment that has been proven to provide significant benefit in reducing morbidity and mortality. There are many clinical trials for numerous different therapeutic agents currently underway. By looking back and measuring successful strategies from previous pandemics in addition to carrying out ongoing research, we provide ourselves with the greatest opportunity to find treatments that are beneficial. It is

reasonable that we continue to work together as a global community to explore different treatment modalities.

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