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Bonnie Ky, MD, MSCE, Douglas L. Mann, MD

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COVID-19 Clinical Trials: A Primer for the Cardiovascular and Cardio-Oncology Communities

1 Bonnie Ky, MD, MSCE
2 Douglas L. Mann, MD

1 Department of Medicine, Division of Cardiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA
2 Department of Medicine, Division of Cardiology, Center for Cardiovascular Research, Washington University School of Medicine, St. Louis, MO

Address for Correspondence:

Bonnie Ky, MD, MSCE
University of Pennsylvania School of Medicine
Smilow Center for Translational Research
3400 Civic Center Boulevard, 11-105
Philadelphia, PA 19104
bonnie.ky@pennmedicine.upenn.edu

Douglas L. Mann, MD
Center for Cardiovascular Research
660 S. Euclid Ave, Campus PO Box 8086
Washington University School of Medicine
St. Louis, MO 63110
dmann@wustl.edu
Abstract

The COVID-19 pandemic has resulted in a proliferation of clinical trials that are designed to slow the spread of SARS-CoV-2, the virus that causes COVID-19. The overwhelming majority of cardiovascular and cancer patients are at increased risk for SARS-CoV-2 infection; accordingly, the cardiovascular and cardio-oncology communities are playing a major role in caring for COVID-19 patients. Many of the therapeutic agents that are being used to treat patients with COVID-19 are repurposed treatments for influenza, drugs that were not effective in Ebola patients, or treatments for malaria that were developed decades ago, and are unlikely to be familiar to the cardiovascular and cardio-oncology communities. Here we have provided a foundation for cardiovascular and cardio-oncology physicians who are on the frontline providing care to COVID-19 patients, so that they can better understand the emerging cardiovascular epidemiology of COVID-19, as well as the biological rationale for the clinical trials that are ongoing for the treatment of COVID-19 patients.
Introduction

The COVID-19 pandemic has resulted in a proliferation of clinical trials that are designed to slow the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. These therapies range from vaccines, to repurposed treatments for influenza, to drugs that were not effective in Ebola patients, to treatments for malaria that were developed decades ago. Recognizing that patients with underlying cardiovascular risk factors, cardiovascular disease, or cancer have an increased risk for adverse outcomes with COVID-19, and recognizing that these vulnerable populations may be enrolled in COVID-19 clinical trials, here we present a critical review of the rationale for the different therapeutics that are currently being employed. As background, we first review the epidemiology of COVID-19, followed by the biology of coronavirus. We then briefly define the complex interplay between the coronavirus and the renin-angiotensin system (RAS), which is directly relevant to the care of the majority of patients with cardiovascular disease or cancer who are receiving drugs that modulate this system. Finally, we review the mechanisms of action the multiple therapies that are currently being studied in clinical trials. Given the breadth of information that is emerging, we will not discuss the role of vaccines.

Epidemiology of COVID-19

The current impact of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unquantifiable. The number of confirmed cases and deaths from the global COVID-19 pandemic increase daily (https://www.statnews.com/2020/03/26/covid-19-tracker/ https://coronavirus.jhu.edu/map.html). While there is a great deal that still remains to be
understood, initial reports from 552 hospitals in China describing 1,099 of the 7,736 COVID-19 infected patients provide some insight into the disease (1). In this multi-center retrospective analysis, the majority were Wuhan residents or had contact with Wuhan residents, although 25.9% were neither. The median age of patients was 47 years (Interquartile range [IQR] 35 to 58), and 41.9% were female. Patients with more severe disease tended to be older, and tended to suffer from at least one comorbidity, compared to those with non-severe disease. In this retrospective analyses, patients commonly received intravenous antibiotics (58.0%). Oseltamivir was administered in 35.8%, systemic steroids in 18.6%, and oxygen in 41.3%. The median duration of hospitalization was 12.0 days, interquartile range 10.0-14.0 days); however, the majority of the patients (93.6%) remained hospitalized at the time of data analyses and as such, the clinical course still largely remains to be defined.

**COVID-19 and cardiovascular complications.** Epidemiologic data thus far suggest that patients with cardiovascular risk factors, including older age; cardiovascular disease; or cancer are more susceptible to infection and suffer from worse clinical outcomes (2). COVID-19 can also directly result in a number of cardiovascular complications, including fulminant myocarditis, myocardial injury, heart failure, and arrhythmia (1,3,4). There have been a number of published case reports of clinically suspected myocarditis with markedly elevated troponin levels, ST-segment elevations on electrocardiogram without obstructive coronary disease in the presence of severely decreased left ventricular systolic function and shock (5), with cardiac magnetic resonance imaging evidence of diffuse myocardial edema and gadolinium enhancement (6). However, in another isolated autopsy report from a patient who suffered from SARS-CoV-2-related pneumonia and cardiac arrest, no obvious histological changes in the myocardium were observed with the exception of few interstitial mononuclear inflammatory infiltrates (7).
Elevated troponin levels have also been observed in those with worse clinical outcomes. In a retrospective, single-center analysis of 416 hospitalized patients with confirmed COVID-19, 19.7% displayed evidence of cardiac injury, as defined by elevated high sensitivity Troponin I levels greater than the 99th percentile upper limit. Those with confirmed cardiac injury tended to be older (median age of 74 versus 60 years) and suffer from hypertension (59.8% versus 23.4%), diabetes (24.4% versus 12.0%), coronary heart disease (29.3% versus 6.0%), heart failure (14.6% versus 1.5%), or cancer (8.5% versus 0.6%) (8).

**COVID-19 in patients with cardiovascular risk factors or disease.** Patients with cardiovascular risk factors or disease are at increased risk for suffering from worse clinical outcomes with COVID-19. In an analysis of 2 cohorts from Jinyintan Hospital and Wuhan Hospital of 191 patients, patients with hypertension, diabetes, coronary heart disease were each at increased risk of mortality upon hospital admission (9). The prevalence of hypertension amongst non-survivors was 48% as compared to 30% in survivors; 31% versus 19% for diabetes, and 13% versus 8% for cardiovascular disease. These comorbidities were also more likely to be present in patients who required intensive care unit admission (2). Other studies, including a recently published meta-analysis of 46,248 infected patients, have corroborated the observation that patients with cardiovascular risk factors or cardiovascular disease have worse clinical outcomes (10) and also suggest that hypertension (17±7, 95% CI 14-22%), diabetes (8±6%, 95% 6-11%) and CV disease (5±4%, 95% CI 4-7%) were prevalent comorbidities amongst infected patients. Recent studies have also demonstrated that overall 19.7% of patients suffer from cardiac injury (8). Age and hypertension were predictors of an increased likelihood of cardiovascular complications, and cardiovascular complications were associated with a 4.26-fold increased risk of death (95% CI 1.92-9.49).
COVID-19 in patients with heart transplantation. There have been case series published on COVID-19 infection in heart transplant recipients. Two confirmed cases suggest similar presentations to non-transplant recipients and both patients demonstrated clinical improvement. A questionnaire of 87 heart transplant recipients in China, of which importantly 96.6% undertook quarantine procedures, did not suggest a markedly elevated rate of SARS-CoV-2 infection in this population (11,12).

COVID-19 in patients with cancer. In a retrospective medical review of 1,524 patients with cancer who were admitted to the Department of Radiation and Medical Oncology in Zhongnan Hospital of Wuhan University from December 30, 2019 to February 17, 2020, the infection rate of SARS-CoV-2 in patients with cancer was 0.79% (95% CI 0.3-1.2%) (13). In contrast, the estimated cumulative incidence of all COVID-19 cases in Wuhan was 0.37%. As a result, the odds of infection in cancer patients were estimated to be 2.31 greater (95% CI 1.89-3.02). Cancer patients who were infected had a median age of 66 years and were more likely to have non-small cell lung cancer (58.3%). Five of these patients were being treated with chemotherapy, immunotherapy, or radiation therapy. Three deaths were recorded.

In a multicenter, prospective cohort study of 2,007 cases from 575 hospitals, 1% of the 1590 COVID-19 cases had a history of cancer (13). This in contrast to an incidence of cancer in the Chinese population of 0.29% per 100,000 people. Again, amongst those infected, lung cancer was most common and patients tended to be older. When compared to patients without cancer, patients with cancer also suffered from an increased risk of adverse events that tended to occur earlier, including admission to the intensive care unit (ICU), need for invasive ventilation, or death, which occurred in 7 of 18 patients (39%), compared to 124 of 1,572 patients without
cancer (8%). Cancer patients who were recently treated with chemotherapy or surgery were also more likely to suffer from clinically severe adverse events.

**The Coronavirus Family**

Coronaviruses (CoVs) represent a large family of hundreds of enveloped, single-stranded, positive sense RNA viruses that establish an infection primarily by targeting the mucosal surfaces of respiratory and intestinal tracts of a wide range of mammals and birds. There are four main sub-groupings of CoVs: alpha, beta, gamma, and delta (14). The seven coronaviruses that are capable of infecting humans include, 229E (alpha coronavirus); NL63 (alpha coronavirus; OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus), SARS-CoV (beta coronavirus) and SARS-CoV-2 (beta coronavirus). The prototype human CoV isolates 229E and OC43 have been causally linked to the common cold. SARS-CoV is the cause of the severe acute respiratory syndrome, or (SARS), whereas MERS-CoV was established as the cause of Middle East Respiratory Syndrome (MERS). SARS-CoV-2 is a novel coronavirus that causes coronavirus disease 2019 (COVID-19). Identification and sequencing of the virus responsible for COVID-19 established that it was a novel CoV (2019-nCoV) that shared 88% sequence identity with two bat-derived SARS-like CoVs (14). Subsequently, 2019-nCoV was shown to share a 79.5% sequence homology with SARS-CoV, and was subsequently renamed SARS-CoV-2 (14). The genome of the coronaviruses encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein (Central Illustration). The S protein is responsible for facilitating entry of the CoV into the target cell (14) (15), and is comprised of a short intracellular tail, a transmembrane anchor, and a large ectodomain that consists of a receptor binding S1 subunit and a membrane-fusing S2 subunit (14).
Coronavirus Virology

Given that far more is known with respect to the virology of SARS-CoV than SARS-CoV-2, and given that these two coronaviruses appear to have some overlapping biology and clinical presentations, we will discuss these two viruses together, with an emphasis on the most recent studies that have revealed unique aspects biological aspects of SARS-CoV-2. We will review viral attachment, entry and replication of SARS-CoV and SARS-CoV-2 in host cells. This discussion will be integrated with a review of the ongoing clinical trials that target these different aspects of the biology of SARS-CoV-2 (see Tables 1-5).

Angiotensin Converting Enzyme 2 (ACE2) is the entry receptor for SARS-CoV and SARS-CoV-2. Viruses enter cells by binding to host cell-encoded proteins that facilitate the entry of the virus into the cell, as well as allow the virus to survive and replicate within the cell. Some viruses, including certain strains of CoVs are capable of down-modulating the entry receptor once they gain access to the cell. Receptor down-modulation is a strategy broadly used by many viruses to escape the immune system, as well as establish the best environment for viral replication and spread (16). Receptor down-modulation may also disrupt many of the natural physiologic functions of the host cell, resulting in cell death leading to organ level dysfunction.

The entry receptor utilized by both SARS-CoV and SARS-CoV-2 is the Angiotensin-Converting Enzyme 2 (ACE2) (Central Illustration), which is type I transmembrane carboxypeptidase with 40% homology ACE. ACE plays a critical role in activation of the RAS, by processing Angiotensin I (Angiotensin 1-10) to Angiotensin II (Angiotensin 1-8), the major effector peptide of RAS, which mediates its effects through selective interactions with G-protein coupled Angiotensin II type 1 (AT1) and type 2 (AT2) receptors (17). ACE, however, has not been implicated in the entry of human coronaviruses into cells.
ACE2 is highly expressed in the mouth, tongue, and type I and II alveolar epithelial cells in the lungs. ACE2 is also abundantly expressed by cardiovascular endothelium, cardiac myocytes, cardiac fibroblasts, as well as epithelial cells of the kidney and testis. The major substrate of ACE2 is angiotensin II, which is cleaved to Ang 1-7 (Figure 1), and functions through association with the G-protein-coupled receptor Mas receptor. The ACE2–Ang (1–7)–Mas receptor axis is regarded as the counter-regulatory arm of the RAS by opposing the effects of the ACE–Angiotensin II axis-AT1. Although the precise role of ACE2 is still being evaluated, studies have shown that ACE2 exerts protective effects in the pulmonary and the cardiovascular systems, where it serves to oppose the deleterious effects of RAS activation (18-20).

Infection with SARS-CoV and SARS-CoV-2 is triggered by binding of the spike (S) protein on the surface of the coronavirus to ACE2 that is expressed on the cell surface. The receptor binding domain of the S protein of SARS-CoV-2 is located on the S1 subunit, which undergoes a conformational change when it binds to ACE2, which facilitates viral attachment to the surface of target cells (15). Binding of SARS-CoV-2 to ACE2 can result in uptake of virions into endosomes (Central Illustration). Viral entry into the cell requires priming of the S protein by the serine protease transmembrane protease serine 2 (TMPRSS2), which cleaves the viral S protein at the S1/S2 and the S2’ site, and allows fusion of viral and cellular membranes (21). The S proteins of SARS-CoV-2 can also use pH sensitive endosomal proteases (cathepsin B and L) for priming and entry into cells. Interestingly, the binding affinity the SARS-CoV-2 S ectodomain to ACE2 is 10- to 20-fold higher than the binding of the SARS-CoV ectodomain to ACE2 (15). The increase in stickiness of the SARS-CoV-2 capsid S protein makes disease transmission more likely, and might explain the increased person-to-person transmission with
SARS-CoV-2 compared to SARS-CoV. Insofar as the viral S proteins are the part of the virus that interacts with the immune system, they may serve as a promising target for vaccines. Relevant to this discussion, convalescent sera from SARS patients have been shown to block the entry of SARS-CoV-2 entry into cultured cells, albeit with less efficiency that SARS-CoV (21). However, monoclonal antibodies raised against the receptor binding domain of the S1 protein of SARS-CoV do not bind to receptor binding domain of the S1 protein of SARS-CoV-2, suggesting that SARS-directed antibodies are not cross reactive, and that SARS-CoV-2 proteins are necessary to develop effective antibodies. Although ACE inhibitors do not inhibit ACE2, Hoffman and colleagues demonstrated that anti-ACE2 antibody prevented entry of viral vectors into cell lines expressing the SARS-CoV-2 S protein (21).

**Interaction of Coronavirus with the Renin Angiotensin System.** An additional layer of complexity to understanding the pathophysiology of the SARS-CoV-2 in humans stems from the complexity of the interactions of CoVs with the RAS (Figure 1), as well as the widespread use of drugs that interfere with the RAS, including angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, or angiotensin receptor neprilysin inhibitors. Each of these drugs has different effects on the expression of the various components of the RAS in different tissue beds. Here we will briefly discuss these important interactions, as well as their implications for the treatment of COVID-19 patients.

Previous studies have shown that SARS-CoV spike proteins induce the expression of a cell surface metalloenzyme termed ADAM (A Disintegrin And Metalloproteinase)-17, which was originally described as the enzyme that cleaves membrane bound tumor necrosis factor (TNF)-\(\alpha\) from the cell surface and allows it be circulate in soluble form of (sTNF-\(\alpha\)) (22). As shown in Figure 1, activation of ADAM-17 results in the proteolytic cleavage of ACE2 (referred
to as shedding) from the cell surface, with the release of the catalytically active soluble ACE2 (sACE2) ectodomains into the circulation (referred to as soluble ACE2) (20,23). A decrease in ACE2 levels on the cell surface would be expected to result in a decrease in the levels Ang 1-7 levels (cytoprotective) and a corresponding increase in tissue levels of angiotensin-II (pro-inflammatory and pro-fibrotic). The importance of SARS-CoV2-induced down regulation of cell surface ACE2 was demonstrated in experimental studies, wherein administration of recombinant human ACE2 protein, genetic deletion of the AT1 receptor or administration of an AT1 receptor antagonist were shown to be protective in acute lung injury models (19,20). These, and other observations have suggested that the use of AT1 receptor antagonists may be beneficial in COVID-19 patients (24), and consistent with this, losartan is currently being tested in randomized, double-blind placebo controlled studies as a potential therapy in hospitalized infected patients (Table 1). Relevant to this discussion, the ACE inhibitors in clinical use do not directly affect ACE2 activity (25). The biological significance of circulating sACE2 is not known. Of note, sACE2 retains its ability to bind the S protein of SARS-CoV and was shown prevent entry of SARS-CoV into cells in vitro (26). Thus, sACE2 may act as a decoy receptor that prevents SARS-CoV-2 from binding to ACE2 on the cell surface. APN01 is a human recombinant soluble ACE2 (hrsACE2) that has been shown to block the early stages if SARS-CoV-2 infections in cell culture and human tissue organoid cultures. (27). APN01 has already undergone safety and tolerability testing in a phase II trial I healthy volunteers (NCT00886353), but at the time of this writing is not being tested clinically in COVID-19 patients.

The recognition that many COVID-19 patients have underlying medical conditions that are treated with angiotensin converting enzyme (ACE) inhibitors and AT1 receptor antagonists (28), coupled with the knowledge that hypertension and diabetes treated with these agents have
increased ACE2 levels (24), has given rise to the concern that pharmacologic upregulation of ACE2 by RAS inhibitors may influence the infectivity of SARS-CoV-2 in patient population that is already at high risk for severe COVID-19 infection (29). However, as noted in a recent review on this topic, the experimental and clinical data often yield conflicting results with respect the role of ACE inhibitors and AT1 receptor antagonists on ACE2 levels in different pathophysiological contexts (30), suggesting the effects on RAS inhibitors on ACE2 are complex and nuanced, and should not be assumed to be the same for all RAS inhibitors, nor should it be assumed that changes in ACE2 levels in the heart or other tissues necessarily reflect changes in ACE2 levels in the lung, which is the portal of entry for SARS-CoV-2. Given that we have limited understanding with respect to the interaction of RAS inhibitors, ACE2 levels and SARS-CoV-2 infectivity in humans, we do not believe that it is possible to make definitive statements that go beyond the joint statement issued on March 17, 2020, by the Heart Failure Society of America/the American College of Cardiology/American Heart Association, who together recommended “continuing RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial” (31).

**Entry of SARS-CoV and SARS-CoV-2 into cells.** The entry of enveloped viruses into host cells occurs through two primary mechanisms: one is direct fusion of the viral membrane with the plasma membrane of the host cells, which allows the virus to directly deliver their genomic material into the cytosol; and the second is that virus hijacks the cell's endocytic machinery, by binding to a cell surface receptor, which then triggers endocytosis of the virus-receptor complex (Central Illustration). In the endocytic pathway, the endocytosed virions are subjected to an activation step within the endosome, which is typically mediated by the acidic environment of the endosome, resulting in fusion of the viral and endosomal membranes, which allows for the
release of the viral genome into the cytosol. Several viruses, including HIV and SARS-CoV use direct membrane fusions at the cell surface or endocytosis to enter cells. As noted above, recent studies suggest that SARS-CoV-2 binds to ACE2, which leads to endocytosis of the receptor-virus complex (21). What is not known at this time is whether SARS-CoV-2 is also capable of directly fusing with the lipid membrane of cells. However, based on the similarities of how SARS-CoV and SARS-CoV-2 behave, it is likely that their modes of entry into cells will be similar. Understanding these differences in cell entry has implications for developing novel therapeutics.

**Therapeutics Targeting Endocytosis.** The entry of SARS-CoV into cells was shown to occur by direct fusion of the viral membranes with the plasma membrane of the host cell (Central Illustration), through a process that requires processing of the viral S protein by TMPRSS2 at or near the cell surface. Processing of the S protein exposes the fusion peptide of the S protein that inserts into the cell membrane, which brings the envelope of the viral membrane into closer approximation with the membrane of the host cell, thereby facilitating fusion (32). At the time of this writing, the uptake of SARS-CoV-2 into cells has been shown to occur through endocytosis of the SARS-CoV-2 – ACE2 complex, which also requires priming of the S protein by TMPRSS2. It is not known whether SARS-CoV-2 also enters though direct fusion.

Based on the evidence linking TMPRSS2-mediated SARS-CoV-2 activation to SARS-CoV-2 infectivity (21,33), the small molecule serine protease inhibitor camostat mesylate may also be an attractive target for clinical trials with SARS-CoV-2 (Table 2). Camostat mesylate has already shown to inhibit replication of influenza and parainfluenza viruses and to prevent the
development of pneumonia and viral myocarditis in infected mice (34). Given that the SARS-CoV-2 S protein is activated by the pH dependent cysteine protease cathepsin L, this processing step may be sensitive to inhibition with drugs that indirectly inhibit cathepsin L activity by interfering with endosomal acidification (e.g. bafilomycin A1), or by compounds which directly block the proteolytic activity of cathepsin L.

It has also been suggested that the antimalarial drugs chloroquine and hydroxychloroquine might exert a potent antiviral effect by virtue of its ability to increase endosomal pH. Inside cells, chloroquine and hydroxychloroquine are rapidly protonated and concentrated in endosomes. The positive charge of the chloroquine increases the pH of the endosome, which prevents cathepsin-induced priming of the viral S protein. Both chloroquine and hydroxychloroquine decrease SARS-CoV-2 replication in cultured cells; however, hydroxychloroquine was more potent than chloroquine (35). In a small single-arm study of patients with confirmed COVID-19, treatment with hydroxychloroquine was associated with a significant difference in clearing of viral nasopharyngeal carriage of SARS-CoV-2 within 3 – 6 days when compared to untreated controls. Azithromycin when added to hydroxychloroquine was significantly more efficient for virus elimination (36). However, both therapies can result in QT prolongation, and as such, caution needs to be exercised when using these therapies together. Chloroquine and hydroxychloroquine can also manifest in cardiotoxicity, including cardiomyopathy, both systolic and diastolic, atrioventricular and bundle branch block (37). As detailed below, Hydroxychloroquine will be used as one of the treatment arms in the World Health Organization (WHO) multi-national SOLIDARTY trial (38), and is also currently being investigated in a number of other studies (Tables 2 and 5). Interestingly, amiodarone, which is a cationic amphiphile, was shown to inhibit Ebola virus infection in vitro in target cells, using
concentrations of amiodarone that overlapped those detected in the sera of patients treated for arrhythmias. Both amiodarone and its main metabolite, monodesethyl amiodarone (MDEA), were shown to interfere with the fusion of the viral envelope with the endosomal membrane, thus blocking viral replication (39). Amiodarone has also been shown to inhibit SARS-CoV infection and spreading in vitro, by altering the late compartments of the endocytic pathway by acting after the transit of the virus through endosomes (40).

**Replication of SARS-CoV in Host Cells.** Because of the exceptionally large size or the coronavirus RNA genome (~30 kb) and the complexity of coronavirus-host cell interactions, coupled with the novelty of the SARS-CoV-2 genome, very little is known regarding SARS-CoV-2 replication in cells, let alone how the virus interacts with the host. Given that anti-viral strategies are being considered for treatment of COVID-19 patients, here we will review what is generally understood about SARS-CoV replication in mammalian cells, recognizing that this information may change as we learn more about SARS-CoV-2 (see Figure 2).

Once the genomic RNA of SARS-CoV is released into the cytoplasm of the host cell, the positive-strand viral RNA is translated on host ribosomes into one large polypeptide termed the replicase, which undergoes proteolytic cleavage to yield proteins that are required from genome replication, including a viral RNA-dependent RNA polymerase (RdRp). The viral RdRp generates a full-length, antisense negative-strand viral RNA template, which is used for replicating positive strand viral genomic RNA, as well as shorter subgenomic negative strand RNAs that serve as templates for synthesizing mRNAs that code for structural proteins of the virus, including the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Translation of viral mRNAs occurs using the host endoplasmic reticulum. Once the viral structural proteins, S, E, and M are translated in the endoplasmic reticulum (ER), they move
along the secretory pathway to the endoplasmic reticulum-Golgi intermediate compartment. There, the viral proteins become encapsulated and bud into membranes containing viral structural proteins. Following assembly and maturation, virions are transported to the cell surface in vesicles and released by exocytosis (41,42).

**Therapeutics for Viral Replication.** There are a number of anti-viral drugs that are being repurposed for the treatment of SARS-CoV2. A partial list of these antiviral drugs are discussed below.

**Nucleoside analogs.** Remdesivir (GS-5734) is a nucleoside analog that exhibits broad anti-viral activity. Remdesivir is a prodrug that is metabolized to its active form GS-441524, which interferes with the action of viral RNA-dependent RNA polymerase, resulting in a decrease in viral RNA production. It is not known, however, whether Remdesivir terminates RNA chains or causes mutations in them. Remdesivir was effective against multiple types of coronaviruses in cell culture and a mouse model of SARS (43); however, it did not show an effect in patients with Ebola. Remdesivir is currently being tested in several clinical trials for hospitalized patients with COVID-19 and pneumonia (**Tables 3 and 5**). Remdesivir is also one of the four treatment arms in the multi-national SOLIDARITY trial, which is WHO sponsored multi-national randomized, open clinical trial to evaluate the safety and comparative efficacy of Hydroxychloroquine, Remdesivir, the combination of Lopinavir and Ritonavir, and the combination Lopinavir and Ritonavir plus interferon-beta (38). SOLIDARITY will use an adaptive design, which will allow for discontinuation of drugs that lack effectiveness, as well as adding new drugs that appear promising. This type of trial design offers flexibility and efficiency, particularly in the identification of early signals related to either efficacy or toxicity, while maintaining study validity (44).
Favipiravir (Avigan®) is another nucleoside analog antiviral drug that inhibits viral RNA-dependent RNA polymerase. Like Remdesivir it is a prodrug that is metabolized to its active form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP). Although Favipiravir has undergone phase III clinical trials for the treatment of influenza, it is not yet approved by the FDA. Japan has granted approval for Favipiravir for treating viral strains unresponsive to current antivirals. In preliminary studies Favipiravir was shown to have more potent antiviral activity than lopinavir/ritonavir (45).

Ribavirin (COPEGUS®) is a prodrug that acts as nucleoside inhibitor. The metabolites of Ribavirin resemble adenosine or guanosine nucleosides that then become incorporated into viral RNA and inhibits RNA-dependent replication in RNA viruses. Ribavirin is currently FDA approved for the treatment of chronic hepatitis C virus infection in combination with peginterferon alfa-2a (PEGASYS®).

**Protease Inhibitors.** Lopinavir is a protease inhibitor class that is used in fixed-dose combination with another protease inhibitor, Ritonavir (Lopinavir/Ritonavir [Kaletra®]) for the treatment of HIV. Results from a randomized, open-label study of 199 hospitalized adult patients with confirmed SARS-CoV-2 infection assigned 1:1 to Lopinavir 400mg-Ritonavir 100mg twice daily for 14 days with standard of care or standard of care alone were recently published (46). All patients had an oxygen saturation of 94% on room air or a ratio of partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) <300. The primary endpoint was time to clinical improvement, where clinical improvement was defined based on an ordinal scale or live discharge from the hospital. The study was designed for 80% power with a 2-sided significance level of $\alpha$ of 0.05 to detect an 8-day difference in median time to clinical improvement. Here, the median time to clinical improvement was 16.0 days (IQR 13.0, 17.0 days) in the Lopinavir-
Ritonavir group compared to 16.0 (IQR 15.0, 18.0 days) with standard care. The mortality at 28
days in the treatment group was similar to that observed in the standard care group (19.2%
versus 25%, difference -5.8%, 95% CI -17.3, 5.7), as was the detectable viral load. However,
there were some suggestions of potential benefit with lopinavir-ritonavir with a shorter ICU stay
(median 6 days versus 11 days) and a shorter time to hospital discharge (median 12 days versus
14 days). As noted, the fixed dose combination of Lopinavir/Ritonavir is one of the treatment
arms in the SOLIDARITY trial (Table 3) (38).

**Immunomodulatory Therapies:** Interferons (IFNs) are cytokines activate the innate immune
system in response to viral infection. Type I interferons (IFN-α/β) are synthesized by most cell
types in the body response to a viral infection, whereas type II interferon (IFN-γ) is produced by
immune cells following antigen stimulation. Both Type I and Type II interferons provoke the
synthesis of proteins that have antiviral and immunomodulatory effects. Recombinant IFN-β has
been shown to inhibit SARS-CoV replication in vitro more effectively than either IFN-α or IFN-
γ (47,48). Interestingly, IFN-γ downregulates the expression of ACE2 on the cell surface and
protects type I pneumocytes from SARS-CoV infection (49). The combination of
Lopinavir/Ritonavir and IFN-β1b is being evaluated in the treatment of laboratory-confirmed
MERS requiring hospitalization (50), and will also be evaluated in the SOLIDARITY trial (38).

A number of additional immunomodulatory agents are also currently being evaluated,
including the IL-6 inhibitor, Tocilizumab, and glucocorticosteroids (Tables 4 and 5), given the
cytokine storm syndrome which has been observed in subgroups with severe COVID-19 (51)
with increased levels of interleukin (IL)-2, IL-6, IL-7, and additional inflammatory cytokines
(52). One meta-analysis suggested that the mean IL-6 levels were 2.9-fold (95% CI 1.17, 7.19)
greater in patients with complicated compared to non-complicated COVID-19 (52). Tocilizumab
(ACTEMRA®) is FDA approved for the treatment of severe cytokine release syndrome in patients treated with CAR T cell therapy and also approved for the treatment of rheumatoid arthritis (53-56). Tocilizumab is a monoclonal antibody that binds the IL-6 receptor, both the membrane bound and soluble forms, thus inhibiting both classic and trans-IL-6 downstream signaling. Similarly, the IL-6 humanized murine chimeric monoclonal antibody Siltuximab, although not FDA approved for the treatment of cytokine release syndrome, has also been used in the treatment of cytokine release syndrome and is also being studied as a potential therapy in severe COVID-19 infections. Siltuximab (SYLVANT®) binds directly to IL-6 and prevents the activation of immune effector cells. Sarilumab (KEVZARA®) is a human monoclonal antibody against the IL-6 receptor that was developed for the treatment of rheumatoid arthritis, that is also being evaluated for severe COVID-19.

There are no systematically obtained clinical data that yet support a benefit to the use of steroids, and some reports have suggested a possible detriment with delayed viral clearance and increased risk of infection with MERS and SARS, although the role of steroids in COVID-19 is an area of active investigation (Table 4) (57).

COVID-19 and Cardiovascular Disease

The COVID-19 pandemic has presented innumerable challenges to health care organizations and health care providers. Given that the vast majority of cardiovascular patients are at high risk for SARS-CoV-2 infection, the cardiovascular and cardio-oncology community will play a major role in caring for COVID-19 patients now and for the foreseeable future. As a community, we have a long tradition of enrolling patients into clinical trials that evaluate therapeutic agents whose mechanism(s) of action is familiar, which has for clinical equipoise when enrolling patients in clinical trials. In the coming months that lie ahead our communities
will be asked to contribute patients to clinical trials where the mechanism of action of the therapeutic agents is less familiar and the knowledge base required for providing care for COVID-19 is accelerating at a dizzying pace. Here we have tried to provide a foundation for cardiovascular physicians who are on the frontline providing care to COVID-19 patients, so that they can better understand the emerging cardiovascular epidemiology of COVID-19, as well as the biological rationale for the plethora of clinical trials that are either being designed or are currently recruiting patients.
Central Illustration

The SARS-CoV-2 virus genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein. The S protein is responsible for facilitating entry of the CoV into the target cell. The routes employed by SARS-CoV include endocytosis and membrane fusion. The route employed by SARS-CoV-2 is via endocytosis; whether SARS-CoV-2 enters cells by membrane fusion is not known. Binding of the spike protein of SARS-CoV to ACE2, lead to the uptake of the virions into endosomes, where the viral spike protein is activated by the pH dependent cysteine protease cathepsin L. Activation of the spike protein by cathepsin L can be blocked by bafilomycin A1 and ammonium chloride, which indirectly inhibit the activity of cathepsin L by interfering with endosomal acidification. Chloroquine and hydroxychloroquine are weak bases that diffuse into acidic cytoplasmic vesicles such as endosomes, lysosomes, or Golgi vesicles and thereby increases their pH. MDL28170 inhibits calpain and cathepsin L. SARS-CoV can also directly fuse with host cell membranes, after processing of the virus spike protein by TMPRSS2, a type II cell membrane serine protease. Camostat mesylate is an orally active serine protease inhibitor. (Key: ACE2 = angiotensin converting enzyme II, TMPRSS2 = transmembrane Serine Protease 2).
(Modified from Simmons G et al, Antiviral Res 2013;100:605-14)
Angiotensin converting enzyme converts angiotensin I (Angiotensin 1-10) to angiotensin II (Angiotensin 1-8), which is the major effector peptide of the renin angiotensin system. Angiotensin II mediates its effects through selective interactions with G-protein coupled Angiotensin II type 1 (AT1R) and type 2 (AT2R) receptors. Angiotensin II is degraded to Ang 1-7 by angiotensin converting enzyme 2, Ang 1-7 binds to the Mas receptor (not shown). The ACE2–Ang (1–7)–Mas receptor axis opposes the effects of ACE–Angiotensin II-AT1-axis. The binding of the SARS-CoV-2 spike protein to ACE2 induces ACE2 shedding by activating ADAM-17. A decrease in ACE2 levels would be expected to result in a decrease in the levels Ang 1-7 levels (cytoprotective) and a corresponding increase in tissue levels of angiotensin-II (pro-inflammatory and pro-fibrotic). TMPRSS2, a type II cell membrane serine protease that activates the S protein of SARS-CoV-2 and allows it to bind to ACE2. (Key ACE = Angiotensin converting enzyme, ACE2 = Angiotensin converting enzyme 2, ADAM-17 = A Disintegrin And Metalloproteinase-17; TMPRSS2 = transmembrane Serine Protease 2. (Modified from Simmons G et al, Antiviral Res 2013;100:605-14)
Figure 2: The replication strategy of SARS-CoV. (a) The SARS-CoV spike glycoprotein attaches to the angiotensin converting enzyme 2 (ACE2) receptor on the cell surface. Upon entering the cytoplasm, the viral core particle, which contains the positive (5'→3') strand genomic RNA, is released into the cytoplasm of the cell (b). The positive-strand viral RNA is translated on host ribosomes to generate a large polyprotein (c) that undergoes proteolytic processing to generate multiple viral proteins, including an RNA-dependent RNA polymerase (RdRp). (d) The RdRp generates a full-length, antisense negative-strand (3'→5') viral RNA strand (d) that serves as template for replicating positive strand viral genomic RNA, as well as shorter negative strand RNAs (e) that serve as templates for synthesizing mRNAs that code for structural proteins of the virus (f), including the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Translation of viral mRNAs occurs using the host endoplasmic reticulum (g). Once the viral structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum, they move along the secretory pathway to the endoplasmic reticulum-Golgi intermediate compartment (h). The viral proteins become encapsulated and bud into membranes containing viral structural proteins, where mature virions become assembled. (i) Following assembly, virions are transported to the cell surface in vesicles and released by exocytosis (k) (ACE2 = Angiotensin converting enzyme, ER = endoplasmic reticulum, ERGIC = endoplasmic reticulum-Golgi intermediate compartment) (Modified from Turner et al, Trends Pharmacol Sci 2004;25:291-4.
References

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Table 1: Select Treatment Trials Targeting RAS*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>NCT Number</th>
<th>Title</th>
<th>Study Population</th>
<th>Targeted Enrollment</th>
<th>Study Design</th>
<th>Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>anti-RAS</td>
<td>NCT04312009</td>
<td>Losartan for Patients With COVID-19 Requiring Hospitalization</td>
<td>Aged ≥ 18 years with presumptive positive laboratory test for SARS-CoV-2 or URI with recent exposure to laboratory-proven SARS-CoV-2 infected person; negative influenza or respiratory panel; new or worsening hypoxia (pulse ox &lt; 95%), randomization within 24 hours of presentation</td>
<td>200</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>OFA Respiratory Score at 28 days</td>
</tr>
<tr>
<td>Losartan</td>
<td>anti-RAS</td>
<td>NCT04311177</td>
<td>Losartan for Patients With COVID-19 Not Requiring Hospitalization</td>
<td>Aged ≥ 18 years with presumptive positive laboratory test for SARS-CoV-2 or URI with recent exposure to laboratory-proven SARS-CoV-2 infected person; negative influenza or respiratory panel; randomization within 24 hours of presentation</td>
<td>516</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>Hospital Admission up to 28 days</td>
</tr>
</tbody>
</table>

*For Full Listing of trials, see https://www.clinicaltrials.gov/ct2/results?cond=COVID-19

Abbreviations: RAS = renin angiotensin system; URI = upper respiratory infection; SOFA = Sequential Organ Failure Assessment
Table 2A: Select Treatment Trials Targeting Viral Cell Entry*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>NCT Number</th>
<th>Title</th>
<th>Study Population</th>
<th>Targeted Enrollment</th>
<th>Study Design</th>
<th>Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camostat</td>
<td>Viral Entry</td>
<td>NCT04321096</td>
<td>The Impact of Camostat Mesylate on COVID-19 Infection (CamoCo-19)</td>
<td>Age 18-110 years, COVID-19 confirmed hospitalized patients (&lt; 48 hours) or if hospital-acquired COVID-19 is suspected, less than 48 hours since onset of symptoms</td>
<td>180</td>
<td>Randomized, Double-Blind Placebo Controlled, Phase IIa Trial</td>
<td>Time to clinical improvement at 30 days</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Viral Entry</td>
<td>NCT04315896</td>
<td>Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA Trial)</td>
<td>Aged 18-80 years, COVID-19 confirmed by RT-PCR in any respiratory sample; severe disease defined by pulse ox &lt; 91%, 3% decline from baseline pulse ox, or need for increased supplemental O₂, mechanical ventilation, or sepsis</td>
<td>500</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>All-cause hospital mortality at 120 days</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Viral Entry</td>
<td>NCT04316377</td>
<td>Norwegian Coronavirus Disease 2019 Study</td>
<td>Age &gt; 18 years, hospitalized, moderately severe disease (NEWS score ≤6); SARS-CoV-2 positive test</td>
<td>202</td>
<td>Randomized, Open Label, Single Arm</td>
<td>Rate of decline in SARS-CoV-2 viral load at 96 hours</td>
</tr>
</tbody>
</table>

*For Full Listing of trials, see https://www.clinicaltrials.gov/ct2/results?cond=COVID-19
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>NCT Number</th>
<th>Title</th>
<th>Study Population</th>
<th>Targeted Enrollment</th>
<th>Study Design</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>NCT04303507</td>
<td>Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting</td>
<td>Age ≥ 16 years healthcare worker or frontline participant with patient contact working in a healthcare facility; inpatient or relative of a patient and likely exposed to COVID-19, agree to not self-medicate with potential anti-virals Exposure to a COVID-19 case within 4 days as either a healthcare worker or household contact or symptomatic COVID-19 case with confirmed diagnosis within 14 days of symptom onset or symptomatic healthcare worker with known COVID-19 contact and within 4 days of symptom onset</td>
<td>40000</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>Number of symptomatic COVID-19 infections</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>NCT04308668</td>
<td>Post-exposure Prophylaxis for SARS-Coronavirus-2</td>
<td>Household contact of index case: currently residing in the same household as an individual evaluated at NYP via outpatient, ED, or inpatient services who (1) test positive for COVID-19, or (2) are defined as suspected cases, or PUI, by the treating physician</td>
<td>30000</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>Incidence of COVID-19 disease at 14 days</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>NCT04318444</td>
<td>Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)</td>
<td>Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)</td>
<td>1600</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>Symptomatic, lab-confirmed COVID-19</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>NCT04318015</td>
<td>Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)</td>
<td>Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)</td>
<td>400</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>Symptomatic COVID-19 infection rate at 60 days</td>
</tr>
</tbody>
</table>

Abbreviations; ED = Emergency Department; PUI = persons under investigations
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>NCT Number</th>
<th>Title</th>
<th>Study Population</th>
<th>Targeted Enrollment</th>
<th>Study Design</th>
<th>Primary Outcome Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umifenovir</td>
<td>Antiretroviral</td>
<td>NCT04260594</td>
<td>Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus</td>
<td>Age ≥ 18 years, Subjects with pneumonia diagnosed as 2019-nCoV infection; Detection of 2019-nCoV nucleic acid positive by RT-PCR in respiratory tract or blood samples; virus gene sequence of respiratory tract or blood samples is highly homologous to the known 2019-nCoV.</td>
<td>380</td>
<td>Randomized, Single arm, Open Label Umifenovir</td>
<td>Negative viral conversion rate at 7 days</td>
</tr>
<tr>
<td>ASC09 + Ritonavir; Lopinavir + Ritonavir</td>
<td>Antiretroviral</td>
<td>NCT04261907</td>
<td>Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection</td>
<td>Age between 18 and 75 years; Lab (RT-PCR) and clinical symptoms confirmed case of 2019-nCoV pneumonia; hospitalized with a new onset respiratory illness (≤ 7 days since illness onset)</td>
<td>160</td>
<td>Randomized, Open Label ASC09/Ritonavir or Lopinavir/Ritonavir</td>
<td>The incidence of composite adverse outcomes, defined by at least one of the following: pulse ox ≤ 93% without oxygen supplementation, PaO₂ to FiO₂ ratio ≤ 300 or RR ≥ 30 breaths per minute assessed at 14 days</td>
</tr>
<tr>
<td>Darunavir + Cobicistat</td>
<td>Antiretroviral</td>
<td>NCT04252274</td>
<td>Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV</td>
<td>Pneumonia caused by 2019-nCoV</td>
<td>30</td>
<td>Randomized, Open Label Single Arm</td>
<td>The viral clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 7</td>
</tr>
<tr>
<td>Lopinavir + Ritonavir; Umifenovir</td>
<td>Antiretroviral</td>
<td>NCT04252885</td>
<td>The Efficacy of Lopinavir Plus Ritonavir and Umifenovir Against Novel Coronavirus Infection</td>
<td>Age 18-80 years; confirmation of SARS-CoV-2 infection by RT-PCR with normal kidney and liver function</td>
<td>125</td>
<td>Randomized, Open Label (1:1:1) to Lopinavir + Ritonavir; or Umifenovir; or Standard Care</td>
<td>The rate of viral inhibition, as determined by RT-PCR at days 2, 4, 7, 10, 14, and 21</td>
</tr>
<tr>
<td>Antiretroviral</td>
<td>NCT Number</td>
<td>Study Title</td>
<td>Eligibility</td>
<td>Intervention Duration</td>
<td>Primary Endpoint</td>
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<tr>
<td>Lopinavir + Ritonavir</td>
<td>NCT04330690</td>
<td>Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial (CATCO)</td>
<td>Age &gt; 6 months with confirmed SARS-CoV-2 by RT-PCR, admitted to hospital</td>
<td>Randomized, Open Label (1:1) of Lopinavir + Ritonavir or Standard Care</td>
<td>Efficacy of intervention at 29 days as determined by 10 point ordinal scale of clinical status</td>
<td></td>
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</tr>
<tr>
<td>Remdesivir</td>
<td>NCT04280705</td>
<td>Adaptive COVID-19 Treatment Trial (ACTT)</td>
<td>Age 18 to 99 years, PCR confirmed novel coronavirus infection by lab assay, Illness as defined by abnormal radiographic imaging, clinical assessment and pulse ox ≤ 94%, requiring O₂, or requiring mechanical ventilation</td>
<td>Adaptive, Randomized, Double-Blind Placebo Controlled</td>
<td>Assessment of clinical status at 15 days rated according to an ordinal scale of death, hospitalization requiring ECMO, hospitalization and requiring ventilation, supplemental O₂, or none, non-hospitalized</td>
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<tr>
<td>Remdesivir</td>
<td>NCT04292899</td>
<td>Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19)</td>
<td>Age ≥ 18 years; confirmation of SARS-CoV-2 infection by RT-PCR ≤ 4 days before randomization; current hospitalization with pulse ox ≤ 94%</td>
<td>Randomized, Open Label Study of Remdesivir 5 days; or Remdesivir 10 days</td>
<td>Proportion of Participants With Normalization of Fever and Oxygen Saturation Through Day 14</td>
<td></td>
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</tr>
<tr>
<td>Remdesivir</td>
<td>NCT04292730</td>
<td>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</td>
<td>Age ≥ 18 years; confirmation of SARS-CoV-2 infection by RT-PCR ≤ 4 days before randomization; current hospitalization with fever, pulse ox ≤ 94%, radiographic evidence of pulmonary infiltrates</td>
<td>Randomized, Open Label Study of Remdesivir 5 days; or Remdesivir 10 days or Standard of Care</td>
<td>Proportion of Participants Discharged by Day 14</td>
<td></td>
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</tr>
</tbody>
</table>

*For Full Listing of trials, see https://www.clinicaltrials.gov/ct2/results?cond=COVID-19

Abbreviations: RT – PCR = reverse transcriptase polymerase chain reaction; Partial arterial oxygen pressure = PaO₂; fraction of inspired O₂ = FiO₂; RR = respiratory rate
Table 4A: Select Treatment and Prophylaxis Trials Targeting the Immune System*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>NCT Number</th>
<th>Title</th>
<th>Study Population</th>
<th>Targeted Enrollment</th>
<th>Study Design</th>
<th>Primary Outcome Measure</th>
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<tbody>
<tr>
<td><strong>Treatment Trials</strong></td>
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<tr>
<td>IFN-alpha1beta</td>
<td>Immunomodulatory</td>
<td>NCT04293887</td>
<td>Efficacy and Safety of IFN-alpha1beta in the Treatment of Novel Coronavirus Patients</td>
<td>Age ≥ 18 years with clinically diagnosed coronavirus pneumonia within 7 days, including RT-PCR evidence of coronavirus and symptoms</td>
<td>328</td>
<td>Randomized, Open Label, Single Arm</td>
<td>Incidence of side effects within 14 days including dyspnea, pulse ox ≤ 94%, and RR ≥ 24 breaths/min</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Immunomodulatory</td>
<td>NCT04273321</td>
<td>Efficacy and Safety of Corticosteroids in COVID-19</td>
<td>Age &gt; 18 years, diagnosis of Novel coronavirus pneumonia (COVID-19)</td>
<td>400</td>
<td>Randomized, Open Label, Single arm</td>
<td>Incidence of treatment failure in 14 days</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Immunomodulatory</td>
<td>NCT04244591</td>
<td>Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure</td>
<td>Age &gt; 18 years, RT-PCR confirmed novel coronavirus infection, Symptoms for more than 7 days, PaO\textsubscript{2}/FiO\textsubscript{2} &lt; 200, Positive pressure ventilation (non-invasive or invasive) or HFNC higher than 45 L/min for less than 48 hours, requiring ICU admission</td>
<td>80</td>
<td>Randomized, Open Label of Glucocorticoid Therapy or Standard of Care</td>
<td>Murray lung injury score at 7 days</td>
</tr>
<tr>
<td>Study Title</td>
<td>Drug</td>
<td>Immunomodulatory</td>
<td>NCT Number</td>
<td>Study Details</td>
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<tr>
<td>Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19</td>
<td>Sarilumab</td>
<td>Immunomodulatory</td>
<td>NCT04315298</td>
<td>Age ≥ 18 years; confirmation of SARS-CoV-2 infection by RT-PCR; current hospitalization with evidence of pneumonia and severe disease, critical disease or multi-organ system dysfunction.</td>
<td></td>
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<tr>
<td>Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia</td>
<td>Siltuximab</td>
<td>Immunomodulatory</td>
<td>NCT04329650</td>
<td>Age ≥ 18 years; confirmation of SARS-CoV-2 infection by RT-PCR; current hospitalization with evidence of pneumonia; maximum O₂ support of 35%.</td>
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</tr>
<tr>
<td>Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)</td>
<td>Tocilizumab</td>
<td>Immunomodulatory</td>
<td>NCT04317092</td>
<td>Age ≥ 18 years; confirmation of SARS-CoV-2 infection by RT-PCR; current hospitalization secondary to pneumonia; pulse ox ≤ 93%, requiring O₂, or requiring mechanical ventilation (invasive or noninvasive).</td>
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</table>

Adaptive, Randomized, Double-Blind, Placebo-Controlled with High and Low Doses

Percentage of patients reporting each severity rating on a 6-point ordinal scale (death, hospitalization requiring invasive ventilation or ECMO, hospitalization on non-invasive ventilation or high flow oxygen, hospitalization requiring oxygen, hospitalization not requiring oxygen, not hospitalized)

Proportion of patients requiring ICU admission at 29 days

Mortality at 1-month

Time to resolution of fever for at least 48 hours without antipyretics for 48 hours up to Day 29
| Tocilizumab | Immunomodulatory | NCT04320615 | A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) | Age ≥ 18 years; hospitalized with COVID-19 pneumonia per WHO criteria; pulse ox ≤ 93% or \( \text{PaO}_2/\text{FiO}_2 < 300 \) | Randomized, Double-Blind Placebo Controlled | Clinical Status Using a 7-Category Ordinal Scale at 28 days |
| Anakinra; Siltuximab; or Tocilizumab | Immunomodulatory | NCT04330638 | Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV- AID) | Age ≥ 18 years; hospitalized with confirmed COVID-19 diagnosis by RT-PCR or other laboratory test; hypoxia defined by \( \text{PaO}_2/\text{FiO}_2 \); CXR or CT scan with bilateral infiltrates | Randomized, Open Label (1:1:1:1) to Anakinra; or Siltuximab; or Anakinra + Siltuximab; or Tocilizumab; or Anakinra + Tocilizumab | Time to Clinical Improvement at 15 days |

**Prophylaxis Trial**

| Recombinant human interferon alpha-1beta and Thymosin alpha 1 | Immunomodulatory | NCT04320238 | Experimental Trial of rhIFNα Nasal Drops to Prevent 2019-nCOV in Medical Staff | Age 18 to 65 years, formally serving as medical staff in Taihe Hospital | Two Arm, Open Label to Interferon Alpha 1b in a Low Risk Group and Interferon Alpha 1b and Thymosin Alpha 1 in a High Risk Group | New COVID-19 diagnosis at 28 days |


**Abbreviations:** RT – PCR = reverse transcriptase polymerase chain reaction; high flow nasal cannula = HFNC; rh IFN = Recombinant human interferon alpha-1beta; ECMO = extracorporeal membrane oxygenation; Partial arterial oxygen pressure = \( \text{PaO}_2 \); fraction of inspired \( \text{O}_2 = \text{FiO}_2 \); RR = respiratory rate; ICU = intensive care unit
<table>
<thead>
<tr>
<th>Table 5: Select Treatment Trials with Multiple Targets*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lopinavir + Ritonavir; Ribavirin; Interferon beta-1b</strong></td>
</tr>
<tr>
<td><strong>Lopinavir + Ritonavir; Hydroxychloroquine</strong></td>
</tr>
<tr>
<td><strong>Remdesivir + Hydroxychloroquine; Remdesivir; Hydroxychloroquine</strong></td>
</tr>
<tr>
<td><strong>Combinations of Oseltamivir, Chloroquine, Darunavir, Ritonavir, Lopinavir, Oseltamivir, Favipiravir</strong></td>
</tr>
<tr>
<td>Drug Combinations</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Favipiravir; Chloroquine phosphate</td>
</tr>
<tr>
<td>Remdesivir; Lopinavir + Ritonavir; Interferon beta-1a; Hydroxychloroquine</td>
</tr>
<tr>
<td>Favipiravir + Tocilizumab</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
</tbody>
</table>


Abbreviations: RT – PCR = reverse transcriptase polymerase chain reaction; NEWS = National Early Warning Score; ICU = Intensive Care Unit; IL-6 = interleukin-6