Therapies Against COVID-19: a Running to a Treatment

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There is no specific drug or therapy against COVID-19. Since the beginning of the pandemic, scientists are running to discover a drug or therapy that can treat the disease. What we found until now are a combined drug and therapies that can mitigate the effects of the disease in the human body and how to manage the patient better. In this article, we tried to join the new discoveries and presented the drugs and therapies and their mechanisms to combat the SARS-CoV-2. We showed the immunomodulators, parasiticides, antiviral drugs (focused on Remdesivir), antimalarial drugs, anti-cytokine drugs focused on the role of IL-6, Reumathological drugs, inhibitors of cell-receptors, antiinflammatory drugs, especially the role of corticosteroids (dexamethasone), antibiotics (azithromycin), anti-thrombotic drugs, blood derivates therapies and alternative therapies currently used against COVID-19. Also, we listed the main results of clinical trials of new therapies presented by Recommended Panel Treatment Guidelines [NIAID-RML (USA)]. We searched the data in the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Excerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews, and original articles in this order. We used 302 articles from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, covid, n-SARS-2, COVID-19, corona virus, coronaviruses, immunomodulators, parasiticides, antiviral, antimalarial, anti-thrombotic and anti-cytokine, antiinflammatory, Reumathological drugs, inhibitors of cell-receptors, antibiotics, blood derivates therapies and alternative therapies, with the tools MeSH (Medical Subject Headings), AND, OR, and the characters [,“,; /., to ensure the best review topics. We concluded that despite there is no treatment or drugs against the COVID-19, a combined therapy can help and mitigate the effects of the disease, helping the immune system to combat the virus.
Keywords: COVID-19. SARS-CoV-2. Therapies. Treatments. New Discoveries.

Introduction

COVID-19 is defined as a sickness caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which was first identified in Wuhan City, Hubei Province, China [1]. It was originally reported to the World Health Organization (WHO) on December 31, 2019, and on March 11, 2020, the WHO ed the COVID-19 outbreak as a global pandemic. The period since then has been one of the most challenging in recent history for doctors, researchers, health companies, and all the governments around the world. Scientists are running on to find treatments, drugs, and vaccines to save lives and cure people.

Notwithstanding, no drugs, biologics or vaccines have yet been approved by the health federal agencies worldwide for prevention or treatment of COVID-19. The drugs' arsenal we have available so far is destined for the management of COVID-19 patients. This article review brings a compilation of promising drugs, therapies and treatment against COVID-19, as well as the treatment guidelines panel from National Institutes of Health from the United States.

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SARS-CoV-2: Virology and Drug Targets [2] (Figures 1 and 2)

As already known, SARS-CoV-2 is able to target cells by viral structural spike (S) protein that attaches to the angiotensin-converting enzyme 2 (ACE2) receptor [3]. After the receptor attachment, the virus particle utilizes host cell receptors and endosomes to penetrate the host cells. A host type 2 transmembrane serine protease, TMPRSS2, aids cell entrance via the S protein [3]. Into the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then produces RNA by its RNA-dependent RNA polymerase. Structural proteins are synthesized conducting to completion of arrangement and release of viral particles [4, 5]. These steps of the viral lifecycle give possible targets for drug therapies. Assuring drug targets involve nonstructural proteins (eg, 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Added drug purposes include viral entrance and immune regulation pathways [6, 7].

The Figure 1 presents the main targets and drugs that have been used in attempt to treat the COVID-19, as well as Figure 2 presents the drugs target and immune response (Figure 3).

Immunomodulators, Drugs of ARDS/ Anticytokines and Other Investigational Therapies [8] (Table 1 attached)

Anti-TNF Agents

TNF-α is one of the most potent proinflammatory cytokines with broad spectrum of actions. Marked elevations reported in many inflammatory conditions including cytokine release syndrome. Serum TNF-α levels found elevated in COVID-19 patients with being more pronounced in more severe patients [9]. SARS-CoV viral spike protein can modulate TNF-α-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, required for the viral entry which is coupled to TNF-α production [10]. The hypothesis is that the use of TNF inhibitors might be effective in blocking viral entry and detrimental effects of exuberant TNF-α, which is observed preclinical studies on severe respiratory syncytial virus and influenza infections [11]. Anti-TNFs lead to higher risks of bacterial, viral and fungal infections, thus their use in COVID-19 needs to be supported with preclinical and clinical studies.

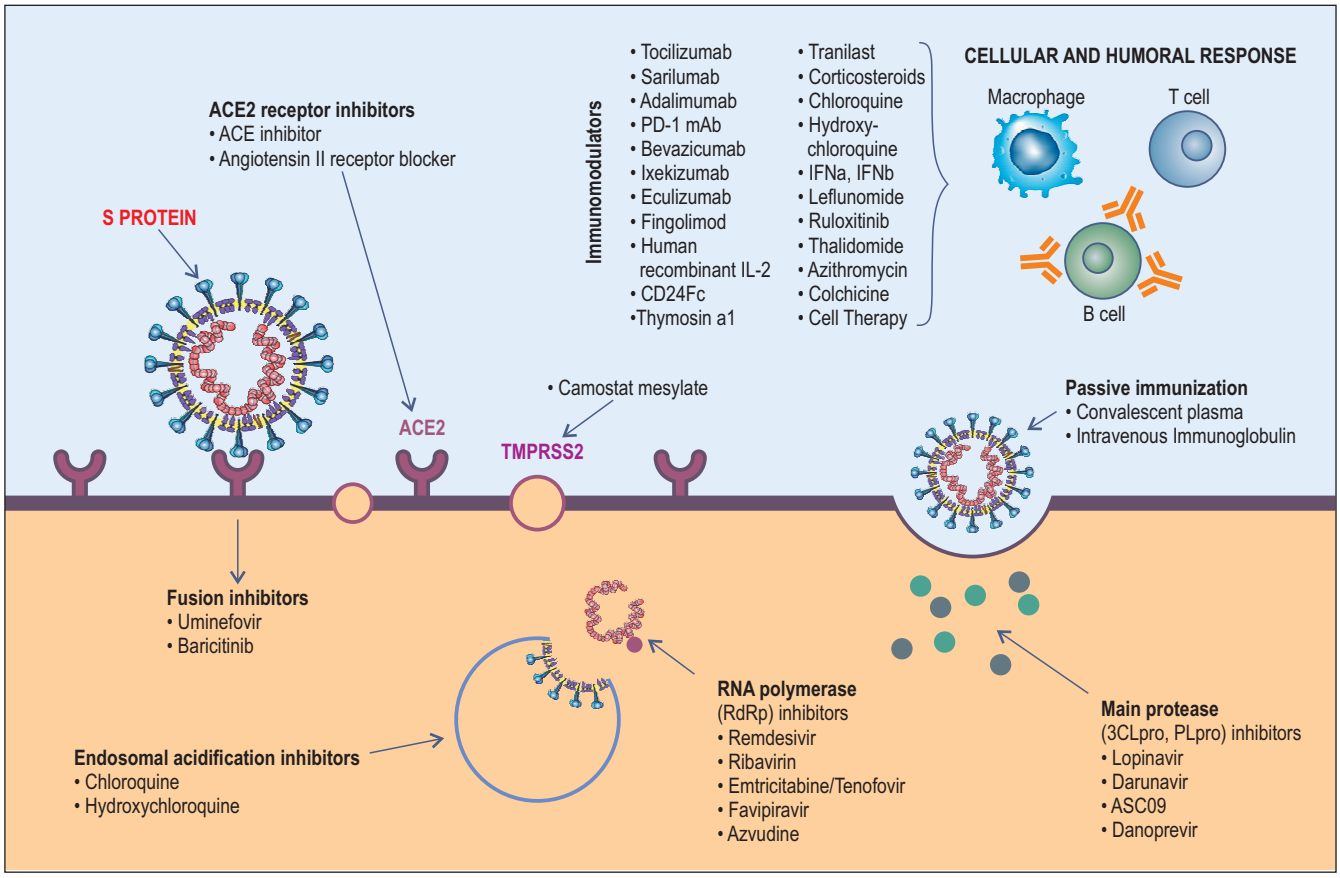
IL-1 Family Antagonists [12]

During the cytokine storm (Figure 4), the three most important cytokines in the IL-1 family are released such as IL-1β, IL-18, and IL-33 [12, 13]. Many studies have shown that a "cytokine storm" relief of IL-6, IL-1, IL-12, and IL-18, simultaneously with tumor necrosis factor-alpha (TNFα) and other inflammatory mediators. The elevated pulmonary inflammatory response may result in increased alveolar-capillary gas exchange, causing oxygenation difficult in patients with severe disease. Investigations that concentrate on the inhibition of IL-1β to decrease the cytokine storm have attracted attention. Anakinra, which is an antagonist of IL-1β, can be applied to treat the cytokine storm caused by infection. Shakoory and colleagues demonstrated that Anakira significantly improved the 28-day survival rate of patients with severe sepsis [14]. According to the Center for Disease Control Guidelines for COVID-19 [15], the data is not sufficient to recommend for or against the use of interleukin (IL)-1 inhibitors for COVID-19 treatment.

Anakira [5]

Nod-like receptor family pyrin domain-containing 3 (NLRP3) is a critical inflammasome in acute protection of the body against a wide variety of noxious stimuli, including RNA viruses [16]. NLRP3 activates caspase-1, a molecule responsible for the activation and exuberant release of IL-1β and IL-18. Previously SARS-CoV has been shown to induce NLRP3 by its ion channel-forming M protein and ORF8b [17]. SARS-CoV-2 is known to induce various cytokines, including

Figure 1. Currently tested therapeutic molecules targeting different steps of SARS-CoV-2 life cycle.



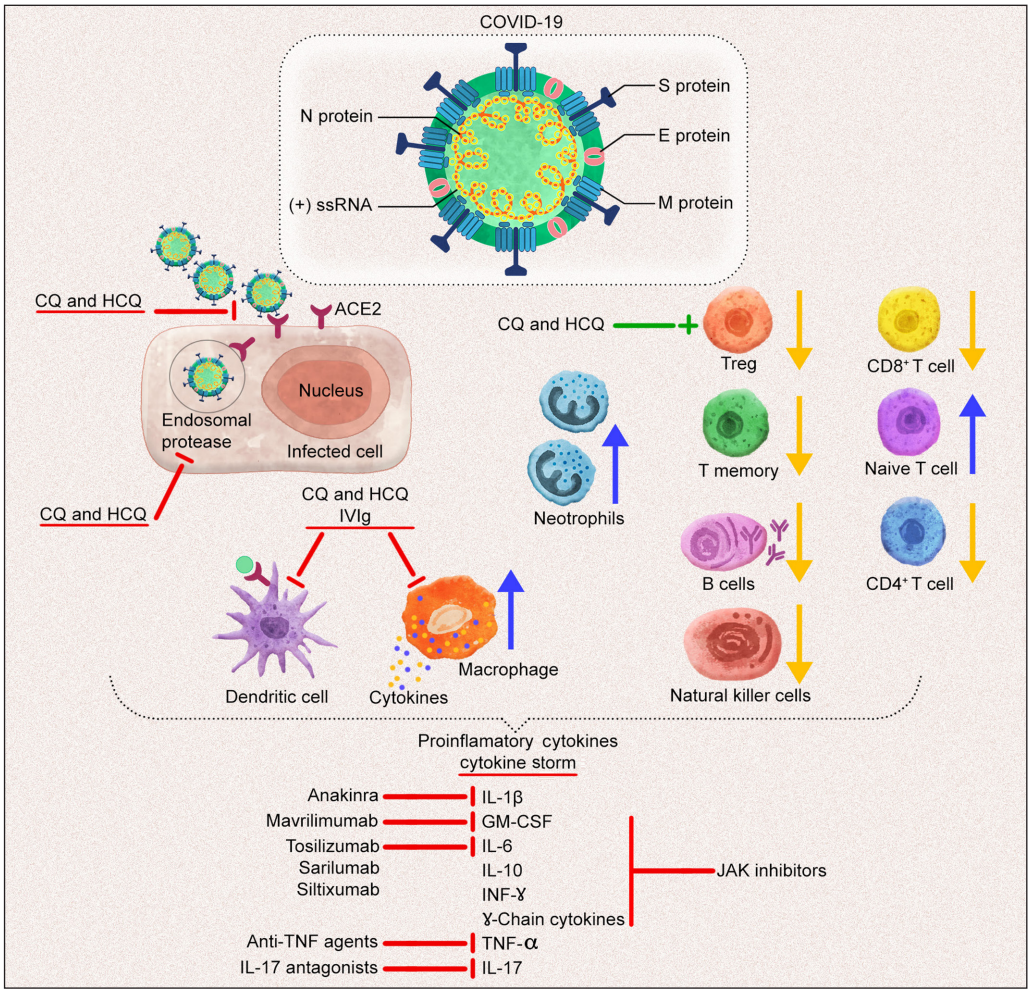
Credit/Source: Adapted from Fragkou and colleagues [7a].

the IL-1 family [18]. The IL-1 family is made up of pleiotropic cytokines, which have roles in inflammation, hematopoiesis, and fibrosis. IL-1β and TNF-α promote vascular permeability and leakage. Both IL-1β and IL-18 fuel cytokine storm and MAS and IL-1 cytokines (except IL-18) can be successfully inhibited by anakinra, as Conti and colleagues' study can attest [19].

Anakinra is a recombinant antagonist of human IL-1 and approved for the treatment of Reumatoid Arthritis (RA) and certain autoinflammatory disorders with recommended doses of 1–2 mg/kg/day with a maximum daily dose of 8 mg/kg [20, 21]. In terms of sepsis and MAS, a previous, highly cited phase III trial, anakinra did not improve 28-day survival rate in sepsis patients and was terminated earlier than expected [22]. Still, a new analysis of data from this trial suggested significant improvement in survival in patients with hepatobiliary dysfunction and disseminated intravascular coagulation (DIC) [14]. Anakinra was administered intravenously at 2 mg/kg/hr for 72 h continuously in this study without safety concerns. Careful monitoring is in order, since this dose is extremely higher than those used in rheumatology routine. There are several anakinra studies registered for COVID-19, testing 100 mg daily subcutaneous injection for 28 days to 400–600 mg/day intravenous for 5–7 days (NCT04339712, NCT04330638).

A recent study from Navarro-Millán and colleagues [23] suggested that Anakira could be benefitial in COVID-19 patients with cytokime storm syndrom when initiated early after onset of hypoxic resiratory failure. Nevertheless, due to the insufficient data on the use of interleukin (IL)-1 inhibitors, such as Anakinra, the Treatment Guidelines Panel against COVID-19 by the National Institutes of Health (NIH) from the United

Figure 2. Drugs target against COVID-19 and immune response.



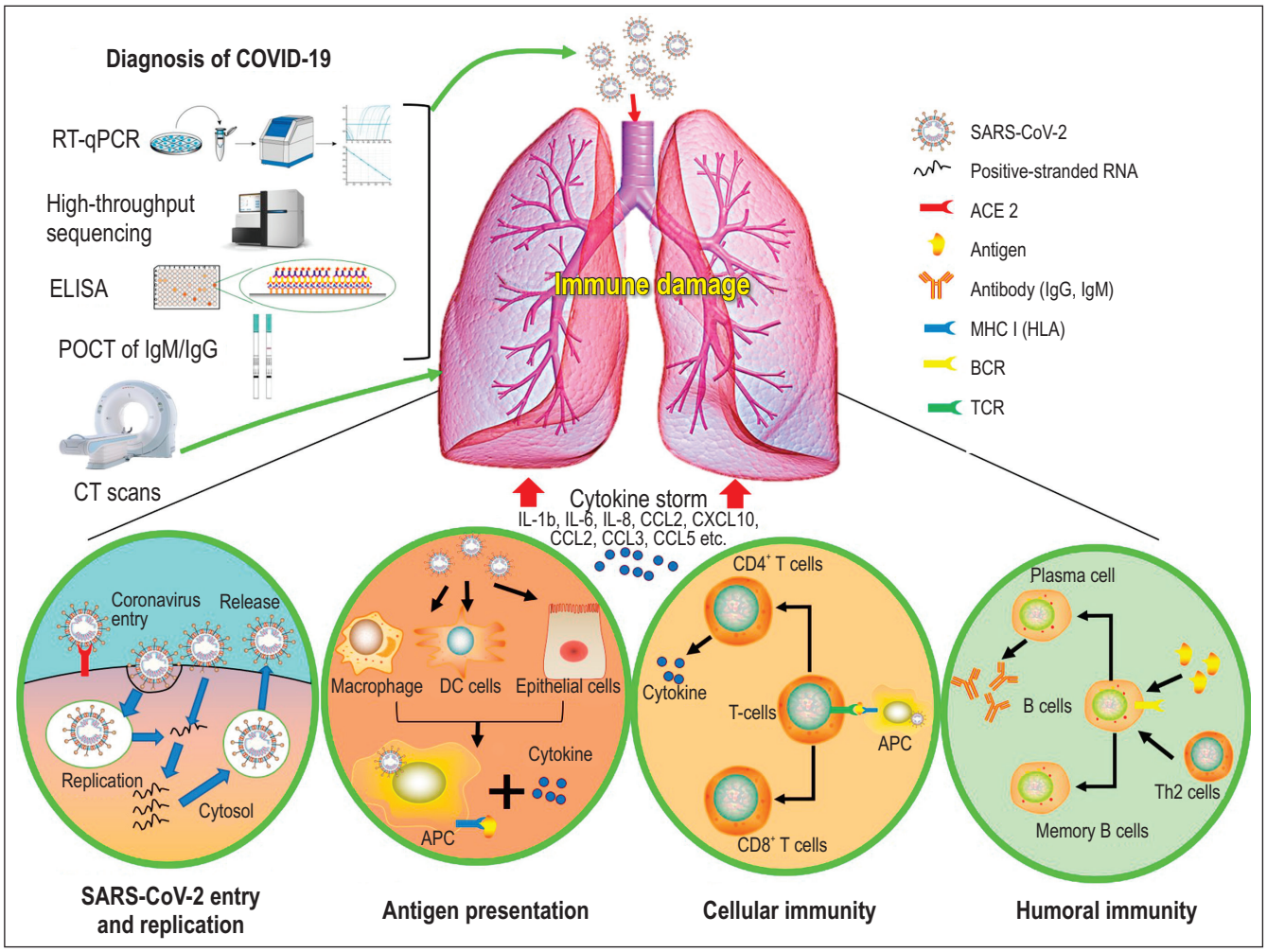
The schematic image of coronavirus (CoV). CoVs, enveloped virus, possess nonsegmented, positive (+) ssRNA genome with structural proteins: Spike (S) glycoprotein, membrane (M) protein, nucleocapsid (N) protein, and envelope (E) protein. SARS-CoV-2 S protein attaches to angiotensin-converting enzyme 2 (ACE2) receptor on the host cell to entry. After the attachment, host endosomal proteases mediate the virus membrane-endosome fusion for the release of the viral genome. Chloroquine (CQ) and hydroxycloroquine (HCQ) block the virus-receptor binding and virus-endosome fusion. Besides CQ, HCQ, and intravenous immunoglobulin (IVIg) inhibit the production of cytokines in macrophages and the antigen presentation in dendritic cells. In COVID-19, the count of neutrophils and leukosytes increase whereas the total count of lymphocytes CD4+ T cells, CD+8 T cells, regulatory T (T reg) cells, memory T cells, natural killer cells, and B cells decrease. Another beneficial effect of CQ and HCQ is increasing the activity of Treg. The aberrant proinflammatory cytokine production is observed in COVID-19. Several immunomodulatory therapies including interleukin (IL)-6 antagonists, granulocyte colony-stimulating factor (GM-CSF) inhibitor, IL-1 antagonists, IL-17 antagonists, and antitumor necrosis factor (TNF) agents might be used for this cytokine storm to resolve and limit the further inflammation and tissue damage (The yellow arrow indicates a decrease in the number of cells; the blue arrow indicates and increase in the number of cells). X (red) This agents are not recommended by FDA, CDC and WHO. Credit/Source: Tufani and colleagues [7b] This work is licensed under a Creative Commons Attribution 4.0 International License.

States does not recommend the use of interleukin (IL)-1 inhibitors against COVID-19 [15].

Anti IL-17 Antagonists

One of the cytokines found abundant in COVID-19 patients is IL-17, which is also associated with severe lung inflammation [8]. IL-17 has wide-ranging proinflammatory effects on induction of cytokines; IL-1β, IL-6, TNF-α; growth factors, G-CSF; chemokines; and matrix metalloproteinases. In a mouse model, it was found that H1N1 cause acute lung injury in an IL-17-dependent manner. It has been postulated

Figure 3. Immune resoponses against COVID-19.



Credit/Source: Li and colleagues [7c].

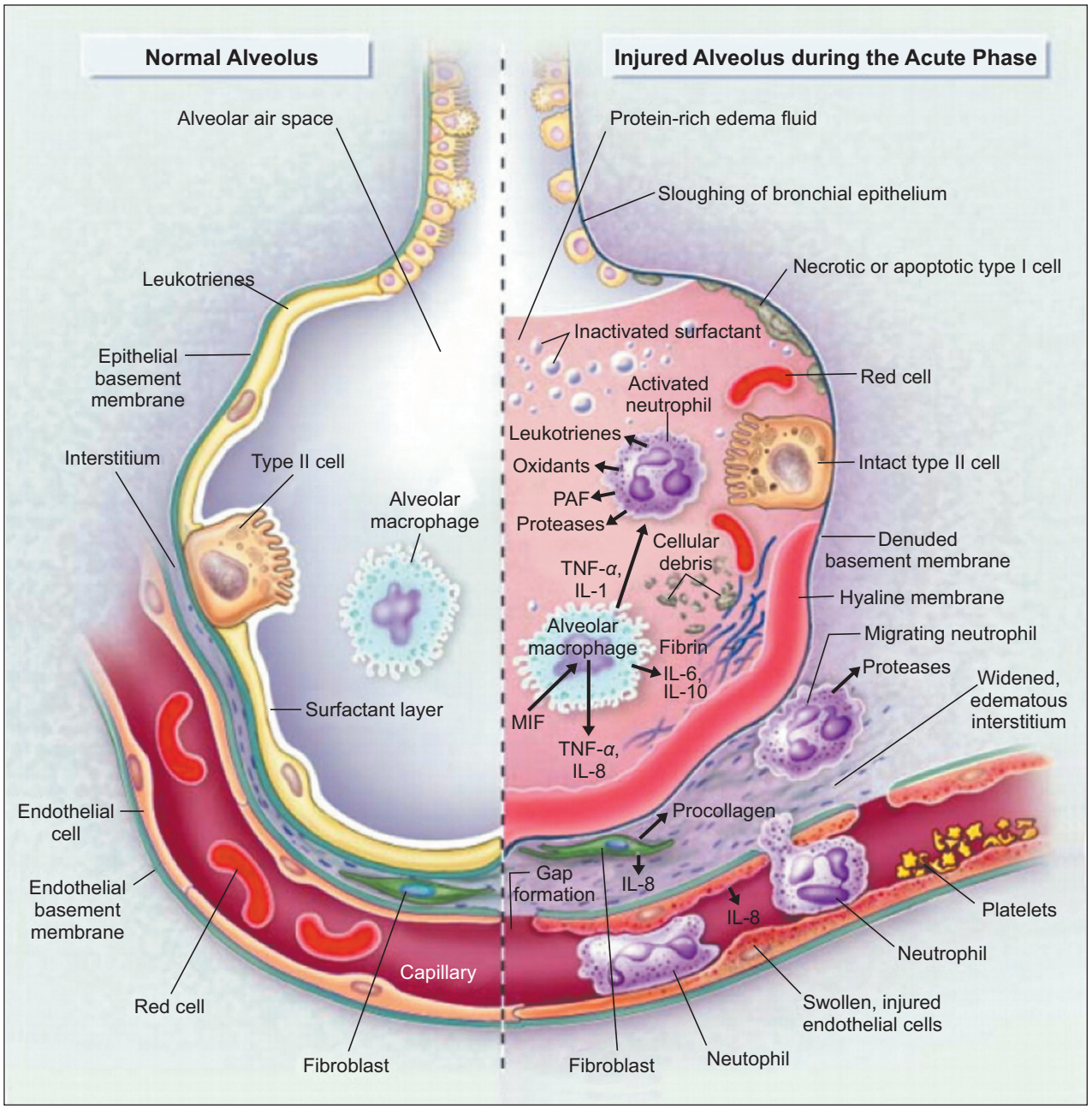
that blocking this cytokine may be effective in reducing SARS-CoV-2 related organ damage [24].

The COVID-19 Treatment Guidelines Panel recommends the use of interferons in patients with severe COVID-19 only in a clinical trial. There are insufficient data to recommend either for or against the use of interferon-beta for the treatment of COVID-19 in any phase of the disease [15].

IFN-λ[12]

IFN-λ primarily activates epithelial cells and reduces the mononuclear macrophage-mediated proinflammatory activity of IFN-αβ [13, 25, 26], and also hinders the recruitment of neutrophils to the sites of inflammation [25]. SARS-CoV and MERS-CoV mainly infect alveolar epithelial cells (AEC), and IFN- λ is able to activate the antiviral genes in epithelial cells, thereby exerting antiviral effects without overstimulating the human immune system. For this reason, IFN-λ may be an ideal treatment, according to Wang and colleagues' study [12]. Some studies have applied pegylated and non-pegylated interferons for the treatment of HCoVs, however, the effectiveness differed significantly due to the use of different treatment regimens. Early administration of interferons has certain benefits in diminishing viral load and enhances the clinical symptoms of patients to a certain limit. Nevertheless, it fails to decrease mortality rates [25, 26].

Figure 4. Cytokine storm and immune responses by SARS-CoV-2 severe infection.



The normal alveolus (Left-Hand Side) and the injured alveolus in the acute phase of acute lung injury and the acute respiratory distress syndrome (Right-Hand Side).
Credit/Source: Bakowitz and colleagues [7c].

IFN-αβ Inhibitors [12]

IFN-αβ restricts viral replication by inducing the IFN-stimulated gene. Nevertheless, IFN-αβ also intensifies diseases through intensifying the recruitment and function of mononuclear macrophages and other innate immune cells. Although an early interferon response has a protecting impact on mice infected with SARS-CoV, delayed IFN-αβ signaling produces an imbalance of the anti-SARS-CoV immune responses in humans. This event means that the

timing of IFN treatment is essential to the outcome of diseases. Based on these results, IFN-αβ receptor blockers or antagonists should be applied in the later phases of critical disease to restrict overexpressed inflammatory responses [27].

Interferon-α (IFN-α) [27, 28]

The IFN-α, a broad-spectrum antiviral drug licensed for the treatment of viral hepatitis, is applied to treat the COVID-19 at a dose of 5 million units through vapor inhalation two times a day alone or in combination with ribavirin (500 mg 2-3 times a day) and antiviral drugs lopinavir/ritonavir (400 mg/100 mg) for a period of 10 days [30]. Earlier, the combination of IFN-α 2a, ribavirin, and lopinavir/ritonavir was used as triple therapy for MERS-CoV in South Korea [31]. It was observed that the SARS-CoV-2 is more susceptible to IFNs as compared to SARS-CoV as the inhalation of IFN-α 2b decreased the infection rate significantly [28] and it can be used for prophylaxis of SARS-CoV-2 infection [33]. However, more studies should be done.

Interferon-β (IFN-β)

The other interferon, IFN-β was first developed for the chronic obstructive pulmonary disorder (COPD) and is recognized to enhance the lung's condition and improve its capacity to combat viral infections. Earlier, it was stated that a reduction in the production of INF-β is straight connected to increased susceptibility of people to develop severe respiratory diseases caused by viral infections [28]. It was also observed that the SARS-CoV-2 infection represses the production of INF-β in the body which results in protection from the immune system [32]. Recently, Synairgen, a UK biotechnology company, has been given the approval to lead a trial using IFN-β on patients with COVID-19 [33]. The advantage with IFN-β is that it can be inhaled alike to IFN-α and can be administered by patients themselves.

Monoclonal Antibodies [1]

Monoclonal antibodies affect inflammatory cytokines and other innate immune responses and represent another possible class of adjunctive therapies for COVID-19. The reason for their use is that the underlying pathophysiology of well-known organ injury in the lungs and other organs because of the overexpressed immune response and cytokine release, or "cytokine storm" [34]. IL-6 seems to be a key role in this dysregulated inflammation based on the first case reports from China [35]. So, monoclonal antibodies against IL-6 could theoretically depress this cytokine process and improve clinical outcomes.

IL-6 Antagonists

IL-6 receptors ubiquitously expressed in almost all immune cells, and IL-6 acts as a master player inducing proliferation and differentiation of immune cells. In healthy individuals, the IL-6 levels in circulation are extremely low and are in the range of 1–5 pg/mL, marked elevations reported in many inflammatory conditions including cytokine release syndrome [35]. Several therapeutic agents have been developed inhibiting the cytokine itself, the signaling via the IL-6 receptor, or its postreceptor downstream signaling pathways (JAK/STAT). Tocilizumab, sarilumab, siltuximab are IL-6 antagonists with different pharmacologic properties. Tocilizumab is approved for the treatment of Rheumatoid Arthritis (RA), juvenile idiopathic arthritis, giant cell arteritis, cytokine release syndrome, and idiopathic multicentric Castleman's disease (iMCD), whereas siltuximab received approval for iMCD and sarilumab for RA only [21].

COVID-19 patients have high plasma IL-6 levels, especially those with more severe disease presentation [36]. IL-6 production can be stimulated by SARS-CoV-2 itself or by stimulation of other immune cell [37]. Indeed, it has been shown that during COVID-19, CD4+T lymphocytes are rapidly activated to differentiate into pathogenic Th1 cells, generating GM-CSF and other proinflammatory cytokines, which further induced activation of monocytes with high expression of IL-6 [38]. In clinical view, there is striking correlation between serum IL-6 levels and SARS-CoV-2 RNAaemia, which strongly indicates worse outcome [38].

Besides the cytokine storm, recent studies in experimentally infected animals suggest a crucial role for virus-induced immunopathological events in causing fatal pneumonia after coronavirus infections [40]. Hence, blocking IL-6 would potentially reduce the detrimental immune response caused by SARS-CoV-2.

However, there is no robust evidence to routinely suggest IL-6 antagonists. A small clinical trial in China examined the effectiveness of tocilizumab in 21 patients who met the criteria for severe or critical COVID-19, including respiratory failure, requiring mechanical ventilation, shock, or admission to the ICU with multiple organ failures. Tocilizumab improved hypoxemia, fever, lymphopenia, CRP, and lung infiltration in most of the patients treated, without serious adverse events [41]. Recently, the favorable outcome of a patient with limited cutaneous systemic sclerosis under treatment with tocilizumab was reported [42].

Since there is an urgent need for the severe COVID-19 treatments, based on these limited data, tocilizumab is included in the treatment algorithms of many countries. The dose and timing for infusions are not determined yet. Numerous studies are ongoing to assess the efficacy of tocilizumab, sarilumab, and siltixumab in several countries. Current practice is to give tocilizumab 4–8 mg/kg (maximum 800 mg) as single infusion. After careful evaluation of disease severity and response to initial treatment a repeat infusion can be administered at the same dose after 12–24 h. IL-6 antagonists increase the risk of infections, therefore must be used in severe patients and at the end of the high viral load phase of COVID-19, along with antiviral treatments [43]. There are other side effects including intestinal perforation and opportunistic infections. Therefore, it is prudent to monitor patients for potential side effects.

According to the COVID-19 Treatment Guidelines Panel, there are insufficient data to recommend either for or against the use of interleukin-6 (IL-6) inhibitors (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19 [15].

Tocilizumab

Tocilizumab (branded as Actemra) is a humanized mAb developed by Roche and Chugai Pharmaceutical for treating RA and systemic juvenile idiopathic arthritis patients. At the time of publishing this article, ClinicalTrials.gov listed 20 planned studies that included tocilizumab treatment arm, all of them at the recruiting stage or earlier. A study published in April 2020 reported that 21 severe or critical COVID-19 patients in China were treated with the compound, with 20 of them recovered at the time of publication and 1 on the way to recovery (but still in ICU). Encouraged by these results, a larger multicenter clinical trial was launched (ChiCTR2000029765) and had about 500 patients treated with tocilizumab already enrolled [44].

Sarilumab

Sarilumab (branded as Kefraza), a humanized mAb, was developed by Regeneron Pharmaceuticals and Sanofi for treatment of rheumatoid arthritis (RA). A phase 2/3 randomized double-blind placebo-controlled clinical trial was planned by Regeneron Pharmaceuticals and Sanofi (and in partnership with Northwell Health's Feinstein Institutes for Medical Research) for March 2020 targeting to enroll 400 COVID- 19 patients, measuring percent change in C-protein (Phase 2 only) and time to improvement on a 7-point scale (based on death and type of hospitalization) in patients with serum IL-6 level above a threshold as primary endpoints.As of the time of this publication, the results of this study have not been made public [45].

Mavrilimumab

As mentioned, GM-CSF is one of the key molecules involved in cytokine storm which is excessively released in COVID-19 patients [46]. Blockage of this growth factor may halt immunopathology caused by virus. Mavrilimumab is a GM-CSF inhibitor developed for the refractory RA [48] and a new trial is investigating its efficacy in COVID-19 (NCT04337216).

Colchicine

Colchicine has been approved for gout and familial Mediterranean fever. In current years, colchicine has attracted attention in the management of cardiovascular diseases by suppressing its inflammatory segment [48]. Its mechanism of activity is thought to be the restraint of tubulin polymerization and microtubule formation and, perhaps, consequences on cellular adhesion molecules, inflammatory chemokines, and the inflammasome. Colchicine may repress the activation of NLRP3 inflammasome and additionally may inhibit directly the synthesis of TNF-α and IL-6 [49]. Trials are investigating the effectiveness of conventional therapeutic doses of colchicine for the treatment of COVID-19 (NCT04322682, NCT04328480, NCT04326790). However, Gendelman and colleagues [51] in a study from April 2020 with an overall sample of 14,520 subjects screened for SARS-CoV-2 infection and 1,317 positive, showed no significant difference in terms of rates of usage of hydroxychloroquine or colchicine between those who were found positive for SARS-CoV-2 and those who were found negative (0.23% *versus* 0.25% for hydroxychloroquine, and 0.53% *versus* 0.48% for colchicine, respectively). These findings raise doubts regarding the protective role of these medications in the battle against SARS-CoV-2 infection.

Janus Kinase (JAK) Inhibitors

JAK inhibitors are potent inhibitors of one or more of the JAK family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the JAK-STAT signaling pathway. The JAK/STAT pathway mediates the effect of many different molecules, including interleukins (IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-15, IL-21, IL-23), IFN-(α, β, γ) and growth factors (GM-CSF, TGF-β, erythropoietin and thrombopoietin) [24]. JAK inhibitors are currently approved for the treatment of RA and psoriatic arthritis and their use in other inflammatory disorders are continuously growing [51]. Many proinflammatory cytokines involved in cytokine storm of COVID-19 might be inhibited by JAK inhibitors.

Baricitinib

Besides above mentioned common properties of JAK inhibitors, baricitinib may block AP-2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) which are host kinases that regulate viral endocytosis, according to an artificial intelligence search of viral characteristics of SARS-CoV-2. This effect is only restricted to baricitinib among other JAK inhibitors and it may block viral entry and assembly of virus particles into pneumocytes in therapeutic doses used in RA [52]. However, these hypothetical views merit further evidence for clinical use both for cytokine storm and COVID-19. Currently, baricitinib (NCT04320277, NCT04340232, NCT04321993), tofacitinib (NCT04332042) and ruxolitinib (NCT04331665) studies are ongoing.

Inhibitors of Mononuclear Macrohage Recruitment and Function [12]

An autopsy of patients with COVID-19 showed many inflammatory cell infiltration in the lungs of the deceased [53]. One potentially powerful treatment approach is to decrease the recruitment of mononuclear macrophages to the site of inflammation by small interfering RNA (siRNA)-mediated silencing of C-C chemokine receptor type 2 (CCR2) to improve the outcome of the disease, which has been demonstrated in animal experiments [54, 55]. Toll-like receptor 7 (TLR7) agonists stimulate mononuclear macrophages to undergo a strong inflammatory response at the time of infections such as HCoV. Hence, TLR7 antagonists may be effective to relieve the storm of inflammatory factors caused by SARS-CoV-2 infection.

Intravenous Immunoglobulin (IVIg)

IVIg is a blood product containing polyclonal immunoglobulin G isolated and pooled

from healthy donors used to treat Immune Thrombocytopenic Purpura (ITP), Kawasaki disease and various inflammatory neurologic and myositis syndromes. It has immunomodulatory functions with unknown mechanism of action. One of the proposed mechanisms is the interaction of IgG-Fc with Fc gamma receptors located on almost all immune cells, resulting in pleiotropic functional consequences including the expansion of regulatory T cell population, phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), immune cell differentiation and maturation, apoptosis, expression of proinflammatory cytokines, and antigen-presentation [56]. Previous studies on SARS and MERS, found that IVIg therapy was effective thus proposing high-dose IVIg as an option for severe COVID-19 patients [57]. There are a few COVID-19 cases which reported efficacy of high dose IVIg [58]. However, its high cost and limited supply restrict its general use. Inferred from rheumatic diseases, COVID-19 patients with pregnancy, secondary infections, marked thrombocytopenia, muscular, myocardial and neurologic manifestations would be better candidates for IVIg treatment. There are several studies already registered for its use in COVID-19.

Inhibitors of Cell Entry of SARS-CoV-2 [58]

Inhibitors of TMPRSS2 Serine Protease

Results from previous studies reveal that diverse viruses, including Ebola virus, SARS-coronavirus (SARS-CoV), MERS-coronavirus (MERS-CoV) and influenza virus employ host cell proteases for activation of their envelope glycoproteins [59, 60]. Cleavage and activation of the spike protein (S protein) of SARS-CoV that is required for membrane fusion and host cell entry is mediated by transmembrane protease/ serine subfamily member 2 (TMPRSS2), an airway and alveolar cell serine protease [61, 62]. Hoffmann and colleagues [63] recently demonstrated that SARS-CoV-2 also employs TMPRSS2 for SARS-CoV-2 S protein priming and S protein-driven cell entry. Using camostat mesilate, a clinically proven and commercial serine protease inhibitor that partially blocks infection by SARS-CoV and HCoV-NL63 in HeLa cell expressing ACE2 and TMPRSS2 [64], it was shown that inhibition of TMPRSS2 in human lung Calu-3 cells by camostat mesilate significantly reduced infection with SARS-CoV-2. Camostat, (FOY-305),[N,N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate] methanesulfate and camostat mesilate (Foipan™), alternatively termed camostat mesylate, (NI-03), (CAS number: 59721−28-7), constitute synthetic serine protease inhibitors that were developed decades ago for the treatment of oral squamous cell carcinoma [65], dystrophic epidermolysis [66], exocrine pancreatic enzyme inhibition [67], and chronic pancreatitis [68]. Camostat mesilate (NI-03) is manufactured as an oral drug by Nichi-Iko Pharmaceutical Co., Ltd., and Ono Pharmaceutical, Japan, with a three times daily dose recommendation of 100 mg–300 mg [69]. In a clinical trial investigating camostat mesilate against dyspepsia associated with non-alcoholic mild pancreatic disease, 95 patients received 200 mg camostat mesilate three times daily for 2 weeks and showed only mild, but no severe adverse effects [70], indicating that camostat mesilate is a well-tolerated drug.

Nafamostat Mesilate (BUIPEL™)

Nafamostat mesilate (Buipel™), (6-amidino-2-naphthyl-4-guanidino benzoate-dimethanesulfonate) (FUT-175), (CAS number: 81525−10- 2), is a clinical proven and synthetic serine protease inhibitor approved in Japan for the treatment of acute pancreatitis, disseminated intravascular coagulation and for anticoagulation in extracorporeal circulation [71, 72]. In a screening approach of about 1,100 drugs approved by the FDA, nafamostat mesilate has been identified to inhibit MERS-CoV S protein-mediated viral membrane fusion with TMPRSS2- expressing lung Calu-3 host cells by inhibiting TMPRSS2 protease activity [58]. Since the S proteins of MERS-Cov

and SARS-CoV-2 share considerable amino acid sequence homology [72, 73], nafamostat mesilate may also inhibit cell entry of SARS-CoV-2. In cell culture experiments with simian Vero E6 cells infected with SARS-CoV-2, nafamostat mesilate was shown to be inhibitive against SARS-CoV-2 infection at EC50 of 22.50 μM [74], suggesting that nafamostat mesilate is able to prevent SARS-CoV-2 infection. In a multicenter, randomized, open-label, phase 2 trial in 19 patients with severe acute pancreatitis, nafamostat mesilate was administered intravenously at a daily dose of 240 mg for 5 days without severe adverse effects.

Inhibitors of Angiotensin-Converting Enzyme 2 (ACE2), Antimalarial/Parasiticide Drugs

SARS-CoV and related coronaviruses directly interact via their S proteins with angiotensin-converting enzyme 2 (ACE2), a host cell exopeptidase and metallocarboxypeptidase that catalyses the conversion of angiotensin I to the nonapeptide angiotensin and the conversion of angiotensin II to angiotensin 1–7, to initiate S protein-mediated cell entry [75, 76]. It was demonstrated recently that also SARS-CoV-2 uses ACE2 as a receptor for S protein-driven host cell entry [62, 73]. Therefore, ACE2 constitute a molecular target to inhibit cell entry of SARS-CoV-2. Unfortunately, ACE inhibitors as standard drugs for the treatment of hypertension and chronic heart failure fail to inhibit ACE2 [77], but a number of other drugs and compounds have been shown to inhibit ACE2.

Antimalarial Drugs (Table 1 attached)

These drugs also fall under three categories based on their mode of action aryl amino-alcohol compound, antifolate compound and artemisinin. Most of these drugs are eliminated gradually from the body remaining for long periods of time after intake. A disadvantage of this drug is that antimalarial drug resistance develops for any drugs under this category [78].

Chloroquine

Chloroquine (CQ), a drug widely used in treating malarial and autoimmune diseases, also confers considerable broad-spectrum antiviral effects even against SARS-CoV [79-81]. A recent study demonstrated that CQ has anti-SARS-CoV-2 activity *in vitro* [82]. A subsequent letter in Bioscience confirmed that CQ is efficacious in treating COVID-19 pneumonia in numerous related clinical trials. CQ therapy resulted in improved pulmonary lesions, shortened disease course, and good outcomes [83]. Given the apparent efficiency displayed by CQ in clinical practice, CQ has been included in the Guidelines for the Diagnosis and Treatment of COVID-19 (7th edition) issued by the National Commission of the People's Republic of China (NHPFC, 2020).

Hydroxychloroquine

Hydroxychloroquine sulfate (HCQ) shares a similar chemical structure and mechanisms of action with CQ but with lower ocular toxicity [84] and has proven efficacious in containing SARS-CoV-2 *in vitro* [85]. CQ and HCQ exert antiviral function through various mechanisms. CQ has been shown to interfere with the glycosylation process of ACE2 in host cells, thereby inhibiting the efficiency of the binding of S protein with ACE2, in turn disrupting the virus/cell fusion process [80] CQ can increase the pH of acidic cellular organelles required for virus entry into host cells [86] In addition to its direct antiviral activity, CQ and HCQ can attenuate major "cytokine storms" (an overreaction of the immune system causing inflammatory "storms") by decreasing cytokine production (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF], etc.) [87].

Chloroquine and Hydroxychloroquine

Chloroquine phosphate (Resochin™) and its derivative hydroxychloroquine (Quensyl™, Plaquenil™, Hydroquin™, Dolquine™, Quinoric™) have been used for decades for the prophylaxis and treatment of malaria and for the treatment of chronic Q fever and various

autoimmune diseases [88], and have been demonstrated as potential broad-spectrum antiviral drugs [80].

Chloroquine phosphate inhibits terminal phosphorylation of ACE2, and hydroxychloroquine elevates the pH in endosomes which are involved in virus cell entry [89, 90], both mechanisms constitute relevant antiviral mechanisms of chloroquine and hydroxychloroquine, respectively. *In vivo*, hydroxychloroquine is metabolized into chloroquine. Chloroquine phosphate has previously been shown to inhibit SARS-CoV infection and spread *in vitro* [89, 91], and results from very recent studies reveal that chloroquine phosphate [83].

However, on June 15, 2020, the FDA removed the use authorization (EUA) for hydroxychloroquine and chloroquine provided to the Strategic National Stockpile to be applied for treating hospitalized patients with COVID-19, except for licensed clinical trials [92]. So, the FDA determined that hydroxychloroquine is unpropitious to be useful in treating COVID-19 in the EUA. Also, due to ongoing severe cardiac adverse events and toxic serious adverse effects, the known and potential advantages of hydroxychloroquine no longer exceed the known and potential risks for patients with COVID-19 [93].

While further clinical trials may proceed to evaluate possible benefits, the FDA determined in the EUA that its use was no longer appropriate.

Additionally, the NIH stopped the Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID) study on June 20, 2020. After the fourth investigation that involved more than 470 participants, the NIH data and safety monitoring board concluded that while there was no harm, the study drug was very doubtful to be advantageous to hospitalized patients with COVID-19 [NIH halts clinical trial of hydroxychloroquine. HIH Media Advisory June 20, 2020]. Hydroxychloroquine and chloroquine are widely used antimalarial drugs that obtain immunomodulatory effects and are consequently also applied to treat autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis). As inhibitors of heme polymerase, they are also considered to have additional antiviral activity via alkalinization of the phagolysosome, which restrains the pH-dependent steps of viral replication. Wang and colleagues [82] reported that chloroquine efficiently inhibits SARS-CoV-2 *in vitro*. The pharmacological action of chloroquine and hydroxychloroquine was experimented with using SARS-CoV-2–infected Vero cells. Physiologically based pharmacokinetic models (PBPK) were conducted for each drug. Hydroxychloroquine was seen to be more potent than chloroquine *in vitro*. Based on PBPK models, the authors suggest a loading dose of hydroxychloroquine 400 mg PO BID, accompanied by 200 mg BID for 4 days [94].

Printed reports deriving from the beginning of the outbreak of COVID-19 have evaluated the potential application of these drugs in controlling cytokine storm in severe patients. Owing to widely differing dosage regimens, disease severity, evaluated outcomes, and the absence of control groups, effectiveness data have been widely inconclusive.

The UK RECOVERY Trial randomized 1,542 patients to hydroxychloroquine and 3,132 patients to usual care alone. Introductory results determined no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care; hazard ratio 1.11 [95% CI, 0.98-1.26]; $p = 0.10$). There was also no proof of useful effects on hospital stay duration or other outcomes [95].

A multicenter, randomized, open-label trial in Brazil discovered no improvement in 504 hospitalized patients with mild-to-moderate COVID-19. The application of hydroxychloroquine, alone or with azithromycin, did not change clinical status at 15 days compared with standard care. Prolonged QTc interval and raised liver enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin than in those who were not taking either agent [96].

An observational study, conducted between March 1, 2020, and April 22, 2020, with follow-up through May 5, 2020, with 2,512 hospitalized patients in New Jersey with confirmed COVID-19 patients presented 547 deaths (22%) and 1,539 (61%) discharges; and 426 (17%) remained hospitalized. From them, who took at least one dose of hydroxychloroquine totaled 1,914 (76%), and those who received hydroxychloroquine plus azithromycin totaled 1,473 (59%). No significant differences were recognized in associated mortality among patients receiving any hydroxychloroquine during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), hydroxychloroquine alone (HR, 1.02 [95% CI, 0.83-1.27]), or hydroxychloroquine with azithromycin (HR, 0.98 [95% CI, 0.75-1.28]). The 30-day unadjusted mortality rate in patients taking hydroxychloroquine alone, azithromycin alone, and the combination of these drugs, or neither drug was 25%, 20%, 18%, and 20%, respectively [97].

After these studies, the WHO stopped the hydroxychloroquine arm of the Solidarity Trial and then removed its application completely as of July 4, 2020 [98]. The FDA announced a safety alert for hydroxychloroquine or chloroquine use in COVID-19 on April 24, 2020, and removed its use in EUA on June 15, 2020 [99]. "The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII). The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI). As well as, The COVID-19 Treatment Guidelines Panel recommends against using hydroxychloroquine plus azithromycin for the treatment of COVID-19, except in a clinical trial (AIII) [15]."

Antiparasiticide

Ivermectin [100]

Ivermectin is a potent anthelmintic drug that was first discovered to hinder interaction between integrase (IN) molecule of human immunodeficiency virus (HIV)-1 and its nuclear transport receptor importin α/β [101]. Further studies exhibit its potential to prevent viral replication of a broad spectrum of viruses, including dengue virus, flavivirus, and influenza [102, 103]. Ivermectin, an antiparasitic drug, has exhibited restraint against SARS-CoV-2 up to 5,000-fold at 48h *in vitro*. Inhibition of IMPα/β1-mediated nuclear import of viral proteins is proposed as the presumable cause of its antiviral action [104]. So, it presented decrease of viral RNA in Vero-hSLAM cells 2 hours postinfection with SARS-CoV-2 clinical isolate Australia/VIC01/2020 *in vitro* [105]. This is an introductory study, which not translate to human use since the efficient dose is not established at this initial phase of discovery. More study is required to conclude if an antiviral effect would be obtained for humans, as the concentrations tested were much higher than what is realized from the normal oral dose [106].

Chaccour and colleagues [107] consider the recent findings regarding ivermectin permit rapid implementation of controlled clinical trials to evaluate efficacy against COVID-19. They also are worried about ivermectin-associated neurotoxicity, particularly in patients with a hyperinflammatory event possible with COVID-19. In addition, drug interactions with potent CYP3A4 inhibitors (eg, ritonavir) warrant careful consideration of coadministered drugs. Lastly, data infers that ivermectin plasma levels with significant action against COVID-19 might not be obtained without potentially toxic raises in ivermectin doses in humans. More data is needed to assess pulmonary tissue levels in humans [107, 108]. And, also, it seems that ivermectin does not interfere with the severity and mortality rate of patients.

Cepharanthine/Selamectin/Mefloquine Hydrochloride

The triple combination of cepharanthine (an anti-inflammatory alkaloid from Stephania cepharantha Hayata), (CAS number: 48,104,902), selamectin (an avermectin isolated from Streptomyces avermitilis and used as an anti-helminthic

and parasiticide drug in veterinary medicine), (CAS number. 220119−17-5), and mefloquine hydrochloride (Lariam™, used for the prophylaxis and treatment of malaria) [109, 110] has recently been shown to inhibit infection of simian Vero E6 cells with pangolin coronavirus GX_P2V/2017/Guangxi (GX_P2V), whose S protein shares 92.2 % amino acid identity with that of SARS-CoV-2 [111]. It has also been demonstrated that GX_P2V also uses ACE2 as the receptor for viral cell entry. Two libraries of 2406 clinically approved drugs were screened for their ability to inhibit cytopathic effects on Vero E6 cells by GX_P2V, and only the combination of cepharanthine, selamectin and mefloquine hydrochloride was identified as candidate drug combination against SARS-CoV-2 infection [111].

Neutralizing Antibodies Against SARS-CoV-2 [112]

Currently, polyclonal antibodies from recovered SARS-CoV-2-infected patients have been applied to treat SARS-CoV-2 infection, but no SARS-CoV-2-specific neutralizing mAbs have been announced. Researchers are working hard to produce such mAbs and/or their functional fragments as putative prophylactic or therapeutic agents to prevent or treat COVID- 19. Once such antibodies are conceived, the next steps will include *in vitro* testing for neutralizing and/or cross-neutralizing activity, *in vivo* evaluation in animal models for protecting efficiency, preclinical studies, and clinical trials testing the security and efficacy before they are approved for clinical application. Hence, it may take one to many years for such SARS-CoV-2 neutralizing mAbs or their fragments to be available for human use.

However, since SARS-CoV-2 is closely related to SARS-CoV and since their S proteins have high sequence identity [113], researchers have attempted to discover SARS-CoV nAbs with potential cross-reactivity and/or cross-neutralizing activity against SARS-CoV-2 infection. Notably, a SARS-CoV RBD-specific human neutralizing mAb, CR3022, could bind SARS-CoV-2 RBD with high affinity and recognize an epitope on the RBD that does not overlap with the ACE2-binding site [114]. In addition, sera from convalescent SARS patients or from animals specific for SARS-CoV S1 may cross-neutralize SARS-CoV-2 infection by reducing S protein-mediated SARS-CoV-2 entry [63]. Moreover, SARS-CoV RBD-specific polyclonal antibodies have cross-reacted with the SARS-CoV-2 RBD protein and cross-neutralized SARS-CoV-2 infection in HEK293T cells stably expressing the human ACE2 receptor, opening avenues for the potential development of SARS-CoV RBD-based vaccines that might eventually prevent SARS-CoV-2 and SARS-CoV infection [115]. It is also possible that SARS-CoV RBD-targeting nAbs might be applied for prophylaxis and treatment of SARS-CoV-2 infection in the current absence of SARS-CoV-2-specific vaccines and antibodies. However, robust testing lies ahead.

Convalescent Plasma [116] (Table 1 attached)

In this procedure, plasma or purified monoclonal antibodies generated against COVID-19 are collected from recovered patients and delivered to new patients as treatment. From 20 January to 25 March 2020, convalescent plasma treatments were administered to five critically sick COVID-19 patients in Shenzhen, China [117]. In this study, patients took convalescent plasma with a SARS-CoV-2-specific antibody between 10 and 22 days after admission. Among the five patients, four of them presented a reduced score in sequential organ failure assessments and viral loads. Their viral test also became negative within 12 days after the transfusion. These four patients were also removed from mechanical ventilation within 2 weeks of treatment. Lastly, three patients were discharged from the hospital in approximately 50 days. Although this trial has a small sample size, the results of convalescent plasma treatment are still hopeful. This method has been suggested as a treatment option in the US [118].

A Cochrane review of convalescent plasma use in patients with COVID-19 is perpetually being updated as data emerge. As of July 10, 2020, the review included 20 studies with 5,443 participants, of whom 5,211 received convalescent plasma. Among these studies was one randomized controlled trial with 103 participants (52 received convalescent plasma). The authors of this review expressed doubt as to the advantages of convalescent plasma in terms of influencing mortality at hospital discharge, prolonging time to death, or enhancing clinical symptoms at 7 or 28 days [119].

A meta-analysis of 15 controlled studies revealed a significantly lower mortality rate in patients with COVID-19 who received convalescent plasma compared with control groups. Nevertheless, the authors point out that the studies were of very low quality and a moderate or high risk of bias [120].

An open-label study (n = 103) with COVID-19 patients in Wuhan, China, who received convalescent plasma did not result in a statistically significant change in time to clinical improvement within 28 days compared with standard of care [121].

A nonrandomized study transfused patients with convalescent plasma based on supplemental oxygen needs. Supplemental oxygen requirements and survival were compared between plasma recipients and controls. Outcomes determined that convalescent plasma transfusion enhanced survival in non-intubated patients ($p = 0.015$), but not in intubated patients ($p = 0.752$) [122].

Hyperimmune Globulin Therapy [123]

Extending experimental findings of CoV in animal models [124] to infer the risk of antibody-enhanced immunopathology in humans is more nuanced. There are likely major differences between vaccine induced *vs* infection-induced antibodies. It is well known that innate immune response drives adaptive immune responses [125-127]. As SARS-CoV-2 infection is known to induce cytokine and chemokine expression, convalescent COVID-19 patients would likely produce antibodies that are qualitatively and quantitatively different to those elicited by vaccination alone. Although vaccines could also elicit innate immune responses, the magnitude would likely be significantly lower than those found in acutely ill COVID-19 patients since the disease is probably mediated by a pro-inflammatory cytokine response [50]. Moreover, the antigenic burden of wild-type SARS-CoV-2 infection can be expected to be significantly greater than those derived from vaccination. The level of such antigenic burden is known to drive adaptive immune responses, including neutralizing antibody titers [128, 129]. Consequently, extending findings from vaccine studies to infer the risk from hyperimmune globulin ignore the possibility of differences between the quality and titer of antibodies produced from infection and vaccination. This same explanation was also found to underpin how inactivated measles vaccination increases the risk of atypical pneumonia [130].

Early anecdotal reports that infusion of convalescent plasma to acutely ill COVID-19 patients suggest the potential of hyperimmune globulin as a treatment to halt the progression of infection to severe pulmonary disease. Hyperimmune globulin treatment, besides inhibiting viral infection, could also downregulate pro-inflammatory responses and reduce disease severity in COVID-19 patients. Intravenous immunoglobulin (IVIG) infusion is associated with anti-inflammatory responses [131], including those from viral infection [132]. Mechanistically, how this anti-inflammatory effect is mediated remains to be fully defined. High dose antibodies could bind a number of different inhibitory receptors, including the inhibitory Fc gamma receptor IIB (FcgRIIB) [129, 130], FcgRIIC [135, 137] or other receptors [141] to induce the anti-inflammatory response. Regardless of the mechanism, the presence of neutralizing SARS-CoV-2 antibodies as well as high concentration of total antibodies could produce anti-inflammatory rather than the postulated immunopathology enhancement effects in COVID-19 patients to improve prognosis.

Antiinflammatory Therapy [7]

Corticosteroids

Systemic corticosteroids have broad-spectrum actions on the immune system that may suppress the exuberant systemic inflammatory response that occurs in ARDS. Severe multi-source systemic inflammation is associated with adverse outcomes, so one may think that corticosteroids may of benefit with their broad spectrum immunosuppressive effects. However, evidence has shown that use of corticosteroids delayed viral clearance in SARS and MERS infections, similarly they increased secondary infection rates, mortality and complications of steroid therapy in survivors of influenza pneumonitis [142]. In a randomized controlled trial that included 16 non-ICU SARS patients, "early" (<7 days of illness) hydrocortisone therapy was associated with a higher subsequent plasma viral load. Therefore, corticosteroids should not be used early phases of disease unless there is a clear indication for their use [139]. In SARS infection, some patients showed severe inflammatory features despite reductions in viral load with subsequent seroconversion, suggestive of exuberant immune response independent of viral load [140]. In two small observational study, use of corticosteroids did not show a survival benefit in COVID-19 patients even increased mortality rates when used in high doses [141, 142]. Moreover, corticosteroid use was prolonged SARS-CoV-2 RNA shedding as observed in SARS and MERS infections [143]. In the light of preliminary data, corticosteroids are more likely to function on inflammation-mediated lung injury and interstitial fibrosis at late-stage of ARDS [144]. However, the dose, duration, and timing of corticosteroids must be individualized considering risk-benefit ratio, until results of ongoing well-designed prospective cohort studies obtained. At present, several studies are registered to assess the efficacy of corticosteroids in COVID-19 [145].

Methylprednisolone

As a potent anti-inflammatory and anti-fibrotic drug, low doses of methylprednisolone (DEPO-Medrol or SOLUMedrol) have the potential to prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia [138, 145]. Recently, many medical researchers believe that corticosteroids, especially methylprednisolone, may improve dysregulated immune response caused by sepsis (possible complication of infection with COVID-19) and increase blood pressure when it is low [146]. Specifically, in a retrospective cohort study, 201 patients with confirmed COVID-19 who developed ARDS were treated with methylprednisolone (1–2mg/kg daily IVfor 5–7days) and the results showed that treatment with methylprednisolone may be beneficial for patients who develop ARDS in the reduction of the risk of death. Briefly, of those patients with ARDS who received methylprednisolone treatment, 23 of 50 (46%) patients died, while those who did not receive methylprednisolone, 21 of 34 (61.8%) died [147]. In another study, 46 patients with severe COVID-19 that progressed to acute respiratory failure, use of methylprednisolone was associated with improvement in clinical symptoms (i.e., fever, hypoxia) and a shortened disease course in patients who received the drug compared with those who did not [148]. Moreover, according to expert consensus statement from Chinese Thoracic Society, dosage regimen of methylprednisolone should be low to moderate (i.e., ≤ 0.5 to 1 mg/kg daily or equivalent) [149] and the most common regimens of methylprednisolone applied in China were typically 40–80 mg IV daily for a course of 3–6 days [150]. The appropriate dosage (low dose *versus* high dose), place in therapy (early *versus* late), and role for corticosteroids (cytokine storm or comorbidity management) require additional clarity. There is concern that the use of corticosteroids may have deleterious effects (i.e., inhibition of immune response and pathogen clearance) in patients with COVID-19 [138]. One study reported no effect on mortality and decreased viral clearance with the use of corticosteroids [2]. Furthermore, the Infectious Diseases Society of American recommends against the routine use

of corticosteroids in COVID-19. However, they do recommend the use of corticosteroids in the setting of ARDS in the context of a clinical trial [151]. Similarly, the Surviving Sepsis Campaign recommends against corticosteroids in mechanically ventilated patients with acute lung injury in the absence of ARDS [152]. However, they provide a recommendation for the use of corticosteroids in patients with ARDS acknowledging the weak level of evidence.

Dexamethasone (Table 1 attached)

Dexamethasone has demonstrated utility on ARDS by decreasing ventilator days and mortality on severe ARDS in patients without COVID-19 [153]. RECOVERY, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, revealed that the mortality rate was lower among patients who were randomized to take dexamethasone than with those who took the standard of care (SOC). This benefit was noted in patients who needed supplemental oxygen at enrollment. No advantage of dexamethasone was seen in patients who did not need supplemental oxygen at enrollment [154]. According to the COVID-19 Treatment Guidelines Panel [15]:

"• On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (discussed below), the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who are mechanically ventilated (AI) and in patients who require supplemental oxygen but who are not mechanically ventilated (BI).

- The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI).
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (see Additional Considerations below for dosing recommendations) (AIII)."

Nonsteroidal Antiinflammatory Drugs (NSAIDs) [7]

An association between ibuprofen and more serious outcome in COVID-19 patients was hypothesized, however, with very low evidence [155]. In an *in vitro* study, another NSAID, indomethacin, was announced to have a direct antiviral impact on SARS-CoV by interfering with viral RNA synthesis, independent of cyclooxygenase inhibition. A trial is currently selecting patients to define the efficacy of naproxen for its potential synergy with viral nucleoproteins (NCT04325633). Hence, although evidence is insufficient, indomethacin or naproxen could be favored over other NSAIDs when indicated [156].

Antithrombotic Therapy [144]

Due to plaque rupture (i.e., type 1 MI) [158], dual antiplatelet therapy, and full-dose anticoagulation should be administered, unless there are contraindications according to the American College of Cardiology (ACC)/American Heart Association (AHA) and ESC guidelines [159, 160]. In patients with high bleeding risk, regimens with short potent antiplatelet agents, such as with clopidogrel, should be considered, since hemorrhagic complications are not rare. Special attention should be also given to drug-drug interactions between antiplatelet agents or anticoagulants and COVID-19 investigational therapies. Major interactions with parenteral antithrombotic agents and COVID-19 investigational therapies are not clearly delimited

Antibiotics

For patients with COVID-19, some physicians manage broad-spectrum antibiotics to all patients with moderate or severe hypoxemia. Other experts administer antibiotics only for specific cases, such as the presence of a lobar infiltrate on a chest x-ray, leukocytosis, high serum lactate level, microbiologic data, or shock. Gram stain

and cultures or testing of respiratory specimens are frequently not available due to concerns about aerosolization of the virus during diagnostic procedures or when processing specimens. There are no clinical trials that have estimated the use of empiric antimicrobial agents in patients with COVID-19 or other severe coronavirus infections. With influenza, empiric antibacterial treatment is strongly prescribed for patients with initial severe disease (i.e., those with extensive pneumonia, respiratory failure, hypotension, and fever) and those who worsen after initial improvement [161]. These recommendations are based on considerations that bacterial superinfections, especially those due to *Staphylococcus aureus* and *Streptococcus pneumonia*, are not unusual and have terrible consequences if not treated immediately. Whether moderate or severe COVID-19 disease should be approached like severe influenza will continue uncertain until more microbiologic and clinical data become available.

Azithromycin (Table 2 attached)

Azithromycin is an antibiotic that can be used to fight many different types of infections caused by susceptible bacteria, such as respiratory infections, skin infections, and sexually transmitted diseases [149, 150]. Moreover, it has been proven to be active *in vitro* against Zika and Ebola viruses and to prevent severe respiratory tract infections when treated to patients suffering viral infection [164, 165]. For the mechanism of action, azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. Previously, azithromycin has been used as adjunctive therapy to provide antibacterial coverage and potential immunomodulatory and anti-inflammatory effects in the treatment of some viral respiratory tract infections (e.g., influenza) [166, 167]. Currently, many trials are testing the effect of azithromycin conjunction with hydroxychloroquine on the course of disease in people with SARS-CoV-2. For example, Pfizer has announced positive data for the use of its azithromycin (Zithromax) drug, along with hydroxychloroquine, in a COVID-19 clinical trial that was performed in France. In brief, the clinical trial was conducted to assess hydroxychloroquine in 20 patients, 6 of which were co-administered with azithromycin. Compared with 16 controls and 14 hydroxychloroquine alone group, the 6 patients treated with hydroxychloroquine + azithromycin presented with highest virologic cure rate following 6-day treatment [166]. Three other clinical studies used azithromycin (500 mg on day 1, then 250 mg daily on days 2–5) co-treated with 10- day regimen of hydroxychloroquine (600 mg daily) in an open-label non-randomized study in France (6 pts) [166], open-label uncontrolled study in France (11 pts) [168], and uncontrolled observational study in France (80 pts) [168]. Specifically, Gautret and colleagues reported a 100% viral clearance in nasopharyngeal swabs in their 6 patients after co-treated of hydroxychloroquine and azithromycin [166]. But the findings reported by Molina and colleagues stand in contrast with those reported by Gautret. Molina and colleagues repeated the experiments, thought the rapid and full viral clearance was quite unexpected and found 8 of 11 patients had significant comorbidities [168]. Based on those results, data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in patients with COVID-19 [168]. Furthermore, one must consider the additive cardiac toxicity of hydroxychloroquine and azithromycin. Both agents are known to prolong the QT interval and may potentiate the risk for cardiac events in a population known to have cardiac-related comorbidities.

Antiviral Drugs (Table 2 attached)

Drugs under this category usually follow either of the following three mechanisms in the virus-viral replication inhibition, ion channel inhibition and serine protease inhibition. Commercially available antiviral drugs mostly target the four major groups of viruses: human immunodeficiency virus (HIV),

herpes, hepatitis and influenza [169]. Earlier outbreak episodes of viral infections like SARS-CoV and MERS-CoV as well as hemorrhagic fever viruses like Ebola were treated with this category of drugs [170].

Ribavirin

Ribavirin is a broad-spectrum drug whose therapeutic potential was uncovered during 1972. This antiviral drug is used in the treatment of hepatitis C. It is usually used in combination with interferon α (IFN). This drug, approved by the FDA, competes for the active site of RdRp. Ribavirin scored 109.5 μM of half maximal concentration against SARS-CoV-2 [171].

Sofosbuvir

This drug is also an FDA approved drug against NS5B and acts as a nucleotide polymerase inhibitor used for the treatment of hepatitis C. It was used in combinationwith interferon or RBV. This drug was previously used for the treatment of Zika virus [172].

Remdesivir

Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. Remdesivir attaches to the viral RNA-dependent RNA polymerase, restraining viral replication by RNA transcription. Its activity has been presented in an *in vitro* study against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [82]. In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; and the results showed that remdesivir-treated animals had lower virus levels in the lungs and less lung injury than the control animals [173]. According to The COVID-19 Treatment Guidelines Panel [15], remdesivir stocks are insufficient, so the Panel recommends that it be prioritized for use in hospitalized patients with COVID-19 who need supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

On May 1, 2020, The FDA approved the use of remdesivir for severe COVID-19 (confirmed or suspected) in hospitalized adults and children [174, 175]. A phase 1b trial of an inhaled nebulized version was beginning in late June 2020 to decide if remdesivir can be utilized on an outpatient basis and at earlier phases of COVID-19 [176].

Remdesivir was studied in clinical trials for Ebola virus infections but presented a limited benefit [177]. Remdesivir has been revealed to restrain the replication of other human coronaviruses associated with high morbidity in tissue cultures, including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. Effectiveness has been shown for SARS-CoV and MERS-CoV in animal models [178].

A phase 3 clinical trials are testing remdesivir for the treatment of COVID-19 in the United States, South Korea, and China, and positive results were presented. The drug was prescribed under an open-label use protocol, but the FDA has since changed and permit enlarged access to remdesivir, allowing established places to prescribe the product for multiple patients under protocol without inquiring permission for each. An adaptive randomized trial of remdesivir directed by the National Institute of Health (NCT04280705) was begun first against placebo, but additional therapies can be combined with the protocol as data emerges. The first experience with this study included travelers of the Diamond Princess cruise ship in quarantine at the University of Nebraska Medical Center in February 2020 after turning back to the United States from Japan following an onboard outbreak of COVID-19. Trials of remdesivir for moderate and severe COVID-19 correlated with standard of care and differing treatment durations are continuing.

The preliminary data analysis of these studies of the Adaptive COVID-19 Treatment Trial (ACTT) was declared on April 29, 2020.

The analysis included 1,063 hospitalized patients with advanced COVID-19 and lung involvement, pointing that patients who received remdesivir improved faster than related patients who received a placebo. Introductory results show that patients who received remdesivir had a 31% faster time to recovery than those who took placebo ($p< 0.001$). Especially, the median time to improvement was 11 days in patients treated with remdesivir compared with 15 days in those who took the placebo. Results also proposed a survival benefit by day 14, with a mortality rate of 7.1% in the remdesivir group, associated with 11.9% in the placebo group, but this was not statistically significant [179].

The ACTT results are different from another randomized trial conducted in China. Results from this randomized, double-blind, placebo-controlled, multicenter trial study (n = 237; 158 to remdesivir and 79 to placebo; 1 patient withdrew) observed that remdesivir was not correlated with statistically significant clinical benefits in adults hospitalized with severe COVID-19. Although not statistically meaningful, patients taking remdesivir had a numerically time faster improvement than those receiving placebo among patients with symptoms of the first 10 days or less. The authors concluded that the reduction in time to clinical improvement in those treated first needs confirmation in larger studies [180]. A phase 3, randomized, open-label trial revealed that remdesivir was associated with the higher recovery and reduced odds of death when compared with the standard of care in patients with critical COVID-19.

The recovery rate at day 14 was higher in patients who took remdesivir (n = 312) compared with those who received standard of care (n = 818) (74.4% *vs* 59%; $p< 0.001$). The mortality rate at day 14 was also lower in the remdesivir group (7.6% *vs* 12.5%; $p = 0.001$) [181].

The open-label phase 3 SIMPLE trial (n = 397) in hospitalized patients with severe COVID-19 disease not needing mechanical ventilation exhibited related improvement in the clinical state with the 5-day remdesivir regimen compared with the 10-day regimen on day 14 (OR: 0.75 [95% CI 0.51-1.12]). In this study, 65% of patients who underwent a 5-day course of remdesivir presented a clinical improvement of at least 2 points on the 7-point ordinal scale on day 14, compared with 54% of patients who took a 10-day course. After correcting for inequalities in baseline clinical status, patients taking a 10-day course of remdesivir had a distribution in clinical status at day 14 that was alike to that of patients taking a 5-day course ($p = 0.14$). The study illustrates the potential for some patients to be treated with a 5-day regimen, which could significantly enlarge the number of patients who could be treated with the current stock of remdesivir. The trial is continuing with an enrollment purpose of 6,000 patients [182].

Data presented at the virtual COVID-19 Conference in July 2020 incorporated a comparative analysis of clinical recovery and mortality outcomes from the phase 3 SIMPLE trials *versus* a real-world cohort of patients with severe COVID-19 taking the standard of care. The analysis revealed remdesivir was related to a 62% decrease in the risk of mortality compared with standard of care. Subgroup analyses obtained from these results were alike to different racial and ethnic groups. While these data are important, they need confirmation in prospective clinical trials [183.

Similarly, the phase 3 SIMPLE II trial in patients with moderate COVID-19 disease revealed that 5 days of remdesivir treatment was 65% more likely to yield clinical improvement at day 11 than the standard of care ($p = 0.18$). These data demonstrate that immediate intervention with a 5-day treatment course can significantly better outcomes [183, 184].

Favipiravir

Favipiravir (Avigan) also identified as T-705 was original approved for the treatment of influenza virus this February, and it has the capacity of inhibiting RNA-dependent RNA polymerase in RNA viruses such as SARS-CoV-2 [185]. In

February, a preliminary clinical trial on favipiravir was handled in China on 80 patients and showed better effects compared to lopinavir/ritonavir with minor adverse effects [186]. Another clinical trial with 340 patients in China resulted in highly promising results as the patients taking favipiravir compared to standard care presented released viral load in four days as compared to eleven days in patients taking standard care [187]. Another multicenter, open-labeled, randomized trial in China has compared the efficacy of favipiravir (1,600 mg × 2 on the first day followed by 600 mg × 2 for 9 days) and umifenovir (200 mg × 3 per day for 10 days) and the outcomes showed a higher recovery rate and better clinical results in the patients treated with favipiravir at day 7 [188]. A phase III trial is ongoing in Japan including 100 patients and is presumed to be completed in June.

Nevertheless, Avigan was not that much helpful in critically ill patients and did not reveal encouraging results. It seems that it has to be taken before the viral load peaks in the body. Favipiravir would need government approval for usage against COVID-19.

MK-4482

Another antiviral originally designed to fight the flu, MK-4482 (previously known as EIDD-2801) has had promising results against the new coronavirus in studies in cells and on animals. Sheahan and colleagues [189] presented that the analog ribonucleoside (β-D-N4-hydroxycytidine - NHC; EIDD-1931) has broad-spectrum antiviral activity against the coronaviruses (SARS-CoV-2, MERS-CoV, SARS-CoV), and also a better possible mutations beard of CoVs when compared to the nucleoside analog inhibitor remdesivir. The *in vivo* study with mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801 improved pulmonary function and reduced virus titer and body weight loss. Merck, which has been running the clinical trials on the drug has announced the beginning of the Phase III trial in the next September.

Umifenovir (Arbidol)

Umifenovir (arbidol) showed efficacy in the treatment of influenza virus infection. It is a viral entrance inhibitor to the target cells, without significant side effects. It has revealed highly promising action against SARS-CoV-2 *in vitro* [190]. A randomized, open-labeled, multi-centered clinical trial conducted in China compared the effectiveness and security of favipiravir and arbidol on COVID-19 patients on 7 day's clinical recovery rate. 120 patients were allocated to each group taking favipiravir and arbidol along with standard therapy. The results showed that the 7-day recovery rate for the arbidol group was 55.86% in comparison to 71.43% for the favipiravir group ($p = 0.0199$). Patients with hypertension or diabetes also showed better recovery in the favipiravir group [189]. Currently, three more phase IV clinical trials are designed for arbidol in the treatment of COVID-19. One clinical trial will compare the efficacy of arbidol on 380 patients at Jieming QU, Ruijin Hospital, China in comparison to the standard treatment [191], whereas, the other two would compare the efficacy of arbidol with oseltamivir [192] on 400 patients at Tongji Hospital, China, and carrimycin on 520 patients at Beijing Youan Hospital, China [193, 194].

Oseltamivir and Baloxavir

Oseltamivir and Baloxavir have antiviral activity against influenza. So, they were considered as possible treatment possibilities for COVID-19. This was used in excess in the initial report of the cases in Wuhan, where patients were managed with COVID-19 receiving oseltamivir in addition to broad-spectrum antimicrobials [2]. It is important to note that the application of oseltamivir was not as targeted therapy of SARS-CoV-2 but an option by the lack of knowledge of the causative pathogen at the time of treatment and the hope to empirically treat influenza. The authors do not recommend the use of oseltamivir for COVID-19 in this study, and there are no data suggesting *in vitro* activity of oseltamivir against SARS-CoV-2. The only data evaluating

oseltamivir activity against coronaviruses showed to be ineffective at inhibiting SARS-CoV-1 [195, 196]. Coronaviruses do not utilize neuraminidase, and thus there is no enzyme to be inhibited by oseltamivir.

Nitazonide

Nitazoxanide has shown potent *in vitro* action against SARS-CoV-2, with an EC50 at 48 hours of 2.12 μM in Vero E6 cells [80]. This powerful activity is compatible with EC50 values for nitazoxanide and its active metabolite, tizoxanide, against MERS-CoV in LLC-MK2 cells [197]. Nitazoxanide exhibits broad-spectrum *in vitro* antiviral action against influenza, respiratory syncytial virus, parainfluenza, rotavirus, and norovirus among others in addition to coronaviruses [196, 197]. This broad-spectrum antiviral activity is thought to be due to the mechanism of action, which is based on interference with host-regulated pathways involved in viral replication rather than virus-specific pathways [197]. Due to its broad-spectrum antiviral action, nitazoxanide is being studied for the management of influenza and other acute respiratory infections. Positive data were described in a phase 2b/3 study for the outpatient management of influenza [198]. Three-phase randomized controlled trials in uncomplicated influenza have since been completed (ClinicalTrials.gov Identifier NCT01610245 [March 2018], NCT02612922 [April 2018], and NCT03336619 [September 2019]), although results are still unavailable. Nitazoxanide declined to decrease the duration of hospitalization or the time to symptom alleviation in phase 2 randomized controlled trial in patients with severe acute respiratory illnesses needing hospitalization [199]. Although the *in vitro* activity of nitazoxanide against SARS-CoV-2 is promising, more data are clearly required to define its role in the management of COVID-19.

Anti-HIV Drugs

These drugs are classified into different categories based on their targets reverse transcription, retro-transcription, proteolytic processing, viral-cell fusion, co-receptors interactions and incorporation of proviral DNA into the host genome. Drugs that fall in these categories have been approved by the FDA (Food and Drug Administration) and are now officially used for the treatment of HIV [181, 184].

Lopinavir/Ritonavir

Lopinavir/ritonavir (LPV-r) is a co-formulated human immunodeficiency virus (HIV)-specific protease inhibitor that serves as first-line therapy for HIV [200]. Concomitant use of ritonavir could increase the plasma half-life of lopinavir through cytochrome P450 inhibition in the liver. During the 2003 SARS outbreak, LPV-r was reported to have *in vitro* inhibitory activity against SARS-CoV [201], and combination therapy of LPV-r and ribavirin provided favorable results in treating patients with SARS [202]. Triple combination therapy with LPV-r, ribavirin, and IFN-α has shown clinical effectiveness for MERS [203]. Notwithstanding, a recent open-label randomized study with 199 patients in Wuhan showed that LPV-r monotherapy did not produce any therapeutic benefits for COVID-19 patients compared with standard supportive care, which might be caused by the higher throat viral loads in the LPV-r group, concurrent pharmacologic interventions, and late treatment initiation [204]. The enrolled COVID-19 patients were critically ill, and LPV-r treatment might have been started relatively late. However, in another retrospective cohort study, combination therapy of LPV-r and arbidol was associated with improved pulmonary computed tomography images [205].

Darunavir

Darunavir (Prezista) is another antiviral drug utilized as an HIV-1 protease inhibitor that demonstrated to be hopeful anti-SARS-CoV-2 activity *in vitro* earlier in February in a test that occurred in China. Nevertheless, Johnson and Johnson stated on March 18, 2020, that there is no indication of sustaining the activity of darunavir against SARS-CoV-2.

Darunavir was approved with a boosting agent such as ritonavir or cobicistat [206]. A single-center open-labeled randomized and controlled phase III trial, conducted at Shanghai Public Health Clinical Center (SPHCC) for the efficacy of darunavir/cobicistat association on the 30th day of COVID-19 patients, revealed that the combination was not efficient in decreasing the symptoms or the duration of treatment [207].

Nelfinavir

Nelfinavir, an HIV-1 protease inhibitor, might be effective against SARS-CoV-2 based on a preprint publication that used homology modeling [208], but no clinical data exist.

Stem Cell Therapy (Table 1 attached)

The mesenchymal stem cells (MSC), a relevant portion of the stem cell family, have the potential of self-renewal and multidirectional differentiation, and also have powerful anti-inflammatory and immune regulatory functions. MSC can restrain the irregular activation of T lymphocytes and macrophages, and provoke their differentiation into regulatory T cell (Treg) subsets and anti-inflammatory macrophages, respectively. Also, it can inhibit the secretion of proinflammatory cytokines, such as IL-1, TNF-α, IL-6, IL-12, and IFN-γ, thereby decreasing the event of cytokine storms [209-211]. MSC can secrete IL-10, hepatocyte growth factor, keratinocyte growth factor, and VEGF to relieve ARDS, restore and repair injured lung tissues, and combat fibrosis [211]. Hence, many uses of MSC are presumed to make it a useful method for the treatment of COVID-19.

Other Therapies

Thalidomide

Thalidomide is an anti-inflammatory and an immunomodulatory agent. It was designed to expand T cells, treat inflammation, restrain cell proliferation, and decrease lung injury and pulmonary fibrosis [116, 213]. The main role of thalidomide in COVID-19 is to preserve the lungs from injury induced by immunological reactions. Nevertheless, thalidomide requires to be used with another antiviral agent, since it does not eliminate or suppress viral load. Wenzhou Medical University reported a case that has demonstrated that thalidomide has adjuvant effects in COVID-19 treatment.

Leflunomide [213]

Leflunomide is efficient in improving SARS-CoV-2 clearance and hospital releasing in refractory COVID-19 patients. The addition of leflunomide to SOC (standard of care) did not develop adverse events *versus* SOC. These introductory considerations emphasize a demand for a randomized clinical study of leflunomide against SARS-CoV-2 infection.

Dipeptidyl Peptidase 4 (DPP4; CD26)

Dipeptidyl peptidase 4 (DPP4) is a functional receptor for the emerging human coronavirus via S-protein, as well as ACE2 [215]. The interaction between the virus and the host cell membrane permits for viral S-protein-directed cell-cell fusion and the resultant spread of viral infections [216]. The specific role of DPP4 on COVID-19 persists to be examined. Further research is needed to use DPP-4 as a therapeutic target for COVID-19.

Aminopeptidase N (APN; CD13)

The aminopeptidase N (APN) is associated with broad receptor engagement, which promotes the cross-species transmission of COVID-19 [217]. Earlier studies recognized APN as a surface tag for cancer stem cells in the human liver [218].

Other studies also enabled the development of a poly(ethylene glycol)-poly(lysine) block copolymer-conjugate (Ubenimex) that targets APN especially [219]. So, low doses of APN inhibitors,

including Ubenimex or its derivatives, may be useful for restraining the spread of the virus.

Ulinastatin [12]

Ulinastatin is a natural anti-inflammatory element in the body. It protects the vascular endothelium by restraining the generation and discharge of inflammatory mediators. Ulinastatin is popularly used in clinical practice to treat pancreatitis and acute circulatory failure. Ulinastatin decreases the levels of proinflammatory factors such as TNF-α, IL-6, and IFN-γ, and raises the level of anti-inflammatory factor IL-10 [220]. These actions of ulinastatin promote the balance between proinflammatory and anti-inflammatory responses in humans, thus disrupting the cytokine storm. Animal studies reveal that the anti-inflammatory effect of high-dose ulinastatin is similar to that of hormones [221]. Nevertheless, unlike glucocorticoids, ulinastatin does not restrain immune functions. Consequently, ulinastatin could have a great application in the treatment of COVID-19.

Sirolimus

Sirolimus (rapamycin) is an immunosuppressant that is used to prevent organ transplant rejection and to treat lymphangioleiomyomatosis (LAM) by repressing the mammalian target of rapamycin (mTOR) kinase. It was originally isolated from the bacterium Streptomyces hygroscopicus located on Easter Island (Rapa Nui) [222] and is commercially available as Rapamune (Pfizer). But there is no data against COVID-19. mTOR, and more specifically a protein complex mTORC1 formed by mTOR, plays a key role in viral replication. In an *in vitro* experiment, sirolimus has been shown to affect PI3K/AKT/mTOR pathway which inhibited MERS-CoV activity [223]. A new randomized double-blind placebo-controlled clinical trial (SCOPE) by University of Cincinnati is planned to be conducted between April and September 2020 to test the effect of sirolimus on progression of patients hospitalized with COVID-19 to advanced respiratory support [224]. Studies of patients hospitalized with influenza can further shed light on the antiviral effect of sirolimus. In a randomized clinical trial conducted on 38 patients with confirmed H1N1 pneumonia and on mechanical ventilator support, a group treated with corticosteroids and 2 mg/day of sirolimus for 14 days (N = 19) showed significantly better clinical outcomes compared with the group treated with corticosteroids only, including shorter median duration of ventilator used [225]. Delayed oseltamivir plus sirolimus treatment in pH1N1-infected mouse model further suggested a significant association between the sirolimus treatment and improved outcomes [226]. Additionally, a new trial by the Chinese University of Hong Kong is planned to begin in August 2020 to investigate the effect of sirolimus and oseltamivir on normalization of respiratory status and changes in biomarkers (viral RNA concentration, 10 cytokines/ chemokines and pro-inflammatory mediators) and several other clinical endpoints in influenza patients [227]. At least one in silico study identified sirolimus as one of the 16 potential candidates for treating COVID-19 patients based on data from other human coronavirus infections using network-based drug repurposing model [228].

Sphingosine-1-phosphate Receptor 1 Agonist Therapy

Sphingosine-1-phosphate (S1P) is a signal lysophospholipid that promotes cytokine synthesis and secretion [229]. The S1P receptor signaling pathways significantly inhibit the pathological injury caused by the host's innate and adaptive immune responses. So, this fact reduces the cytokine storm provoked by influenza virus infection [230, 231]. In mouse models of IAV infection, sphingosine-1-phosphate receptor 1 (S1P1) signal transduction in respiratory endothelial cells modulates pathogenic inflammatory responses [231]. Agonists targeting S1P1 restrain extreme recruitment of inflammatory cells, inhibit proinflammatory cytokines and chemokines, and decrease the morbidity and

mortality of IAV [232]. SARS-CoV-2 also principally affects human lung epithelial cells and endothelial cells. Consequently, S1P1 agonists may be possible therapeutic drugs for decreasing cytokine and chemokine responses in those HCoV patients whose cells produced excessive immune responses. An S1 preceptor modulating drug, siponimod, was approved in 2019 to treat multiple sclerosis. However, clinical trials are required to further confirm whether siponimod is an alternative for the treatment of cytokine storm.

The Inhibitory Effect of Oxidized Phospholipids (OxPL)

OxPL improved the production of cytokines/chemokines in lung macrophages through the Toll-like receptor 4 (TLR4)–TIR-domain- containing adapter-inducing interferon-β signaling pathway in a mouse model of influenza A virus (IAV) infection, promoting the occurrence of ALI [234]. Eritoran is a TLR4 antagonist and has antiviral activity and strong immunomodulatory functions. Eritoran dramatically reduces the production of OxPL, inflammatory cytokines, and chemokines in IAV-infected mice, lowering death [234]. Pathogenic human coronaviruses also cause a high accumulation of OxPL in patients' lung tissues, resulting in ALI [233] Thus, it seems that eritoran and other OxPL inhibitors may also be able to alleviate HCoV-induced inflammatory responses.

Mycophenolate Mofetil (MMF)

MMF is widely used for the treatment of severe manifestations of connective tissue disorders and vasculitis syndromes. Mycophenolate exhibited strong antiviral effects on SARS-CoV and MERS-CoV as demonstrated *in vitro* studies, with its interaction with viral proteases [235]. A small clinical study reported efficacy of MMF in combination with IFN-β on MERS patients [236]. However, considering strong immunosuppressant effects of MMF, it is likely to cause more harm than benefit in COVID-19 patients.

Statins

Statins reduce the inflammatory processes of atherosclerosis [237]. Because of this, issues have risen whether statins may be helpful to reducing inflammation related to COVID-19.

This issue has been presented before the studies of patients who took statins to have acute viral infections by COVID-19. Virani [238] presents a brief review of data concerning observational and randomized controlled trials (RCTs) of statins and viral infections. Some observational studies insinuate that cardiovascular outcomes were decreased in patients taking statins hospitalized with influenza and/or pneumonia. RCTs of statins as anti-inflammatory agents for viral infections are poor, and outcomes have been confused. An important point that Virani reported is that no harm was associated with patients who took statins and had COVID-19 in previous trials of statins and viral infections, indicating that patients should adhere to their statin regimen.

Current Clinical Treatment Experience and Recommendations by World Health Organization (WHO), Center for Disease Control and Prevention (CDC), and National Institutes of Health (NIH) (Tables 1 and 2 attached)

The COVID-19 Treatment Guidelines Panel [15] had been developed to informing physicians on how to caring for patients with COVID-19. The references in these Guidelines are based on scientific data and expert evaluation. Each recommendation involves two ratings: a letter (A, B, or C) that designates the strength of the recommendation and a Roman numeral (I, II, or III) that designates the quality of the evidence that confirms the recommendation (Table 3).

Because clinical information about the optimal management of COVID-19 is developing quickly, these Guidelines will be updated periodically as announced data and other authoritative knowledge

become available. Panel members incorporate representatives from federal agencies, health care and academic institutions, and professional societies. Federal agencies and professional societies reproduced on the Panel include:

- American College of Chest Physicians
- American College of Emergency Physicians
- American Society of Hematology
- American Thoracic Society
- Biomedical Advanced Research and Development Authority
- Centers for Disease Control and Prevention
- Department of Defense
- Department of Veterans Affairs
- Food and Drug Administration
- Infectious Diseases Society of America
- National Institutes of Health
- Pediatric Infectious Diseases Society
- Society of Critical Care Medicine
- Society of Infectious Diseases Pharmacists

Alternative Therapies

We would like to mention that all about surrounding this topic need further studies and evidence. We bring them in order to include all therapeutic purposes to COVID-19 infection.

Vitamin C

Vitamin C is a vital nutrient and plays important role in the human body. It can neutralize free radicals and help to prevent or reverse cellular injury as a powerful antioxidant agent. It is also associated with some biological processes, many of which are correlated with the immune system [239]. Furthermore, vitamin C seems to be useful as an antiviral agent, especially against influenza viruses [240]. Many studies revealed that vitamin C positively influences the development and maturation of T lymphocytes and NK (natural killer) cells implicated in the immune response to viral agents. It also contributes to the restraint of reactive oxygen species (ROS) production and to the modulation of the cytokines typically involved in the systemic inflammatory syndrome [241]. Given this background, a phase II clinical trial (NCT04264533) is initiated in China to evaluate high-dose IV vitamin C in ICU patients with severe COVID-19-associated pneumonia [242]. Some hospitals have reported giving infected patients 1500 mg of vitamin C as supportive treatment. High-dose IV vitamin C has been given in the treatment of 50 moderate to severe COVID-19 patients in China [243]. The doses varied between 2 and 10 g per day, given over a period of 8-–10-h IV infusion. The oxygenation index was improved in real time and all the patients eventually recovered and were discharged [243]. Moreover, high-dose (1.5 mg/kg bodyweight) vitamin C has been used for several decades clinically and an NIH panel also documented clearly that this dose regimen is safe and has no major side effects [244].

Nitric Oxid and Epoprostenol

Since patients with pre-existing pulmonary conditions are at higher risk of COVID-19 and should be closely monitored and cared, pulmonary vasodilator agents have been used in some patients for hypoxemia refractory to conventional treatments, but no study has been performed specifically on COVID-19 patients. The Surviving Sepsis Campaign suggested a trial of inhaled pulmonary vasodilator method as rescue therapy in mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies. Inhaled nitric oxide (iNO) and inhaled epoprostenol (iEPO, a naturally occurring prostaglandin) are two common pulmonary vasodilators that have been widely studied [245, 246]. Experience in patients with ARDS indicates that iNO can substantially reduce mean pulmonary artery pressure and improve oxygenation in such patients. Furthermore, *in vitro* evidence of direct antiviral activity against SARS-CoV was studied and the genetic similarity between SARS-CoV and SARS-CoV-2 suggests their potential effectiveness

against SARS-CoV-2 [249]. For iEPO, dosages up to 50 ng/kg per minute have been used [245, 248]-250]. Previous studies reported that to provide a clinically important increase in PaO2 and reduction in pulmonary artery pressure, the most effective and safe dosage appears to be 20– 30 ng/kg per minute in adults and 30 ng/kg per minute in pediatric patients [251]. For iNO, therapy was given for ≥ 3 days (30 ppm on day 1, followed by 20 and 10 ppm on days 2 and 3, respectively, thenweaned on day 4) in a pilot study on SARS-CoV [251]. Additionally, clinical trials evaluating iNO for treatment or prevention of COVID-19 are planned or underway (NCT04305457, NCT04306393, NCT04312243) [252]. And on March 20, 2020, FDA admitted emergency extended entrance allowing its iNO delivery system (INOpulse®) to be quickly applied for the treatment of COVID-19. Lastly, further studies are needed to appraise the potential role of iEPO and iNO in the treatment of COVID-19 patients.

Natural PAK1-Blockers

A specific vaccine is an effective cure for each viral infection. Nevertheless, it demands at least 12-18 months to be prepared according to the WHO. Until then we have to combat the coronavirus with the guidance of the major research Centers and WHO as well as supportive treatments. Also, "alternative" or "unconventional" therapeutics for coronaviral infection, many natural or synthetic PAK1-blockers readily accessible in the market are introduced.

The Bee Product "Propolis"

Propolis is one of the most popular and ancient substances used for medical supportive treatments. It has been adopted as traditional medicine since the ancient Egyptian era. Its properties are both anti-bacterial and anti-viral. In the modern era, propolis was identified as an anti-cancer medicine in the late 1980s by a group at Columbia University in NYC [253]. The major anti-cancer component in propolis turned out to be CAPE, an ester of caffeic acid [253] which downregulates RAC, thereby inactivating PAK1 [254]. Nevertheless, the anti-cancer properties of propolis vary from one product to another, depending on where bees store the extract. The principal anti-cancer ingredient in Brazilian green propolis is artepillin C (ARC), whereas those in subtropical propolis from Okinawa or Taiwan are polyphenols (Nymphaeols), which directly restrain PAK1 [255]. However, all propolis have PAK1-blockers. Since PAK1 is responsible not only for cancers but also for infection with a wide diversity of viruses such as influenza, HIV, papillomavirus, and coronavirus in generally, as well as immune-suppression [256, 257], propolis would be helpful for blocking coronavirus-induced fibrosis in lungs and stimulating the immune system as well. Nevertheless, the power of propolis alters from one product to another, depending on both the chemical nature of components and their content [256-259]. It's suggested daily dose is 1 mL (250 mg) /10 kg (body weight).

Pineal Hormone "Melatonine"

In 1953, Aaron Lerner at Yale University recognized the serotonin melatonin as an anti-melanogenic hormone that originated from pineal glands [260]. Around the last decade, it was found that melanogenesis depends on PAK1 [261]. Melatonin shares a broad diversity of other anti-PAK1 actions such as anti-infectious, anti-inflammatory, anti-cancer, immune stimulative, analgesic, sleepy, among others. Thus, melatonin, a current sleeping pill, could be useful for the therapeutic of coronaviral infection. Russel Reiter, recently highlighted that melatonin is an alternative or adjuvant COVID-19 therapeutic [262].

Glucocorticoid Hormone "Ciclesonide"

Ciclesonide is used to treat inflammatory diseases such as asthma and allergic rhinitis. Concerning the molecular mechanism of its anti-inflammatory effect, it seems that this hormone bars PAK1, mainly for the following purposes: (i)

Table 3. Recommendation rating scheme.

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	III: Expert opinion

Credit/Source: NIAID-RML [15].

An example how the recommendation scheme works, there are for blood-derived products under evaluation for the treatment of COVID-19. According to the Papel, there is a summary recomendations: (*Last Updated: July 30, 2020*) [15].

Summary Recommendations
There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19: • COVID-19 convalescent plasma • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins
The Panel recommends against the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial: • Mesenchymal stem cells (AII) • Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

inflammation requires PAK1 [263], and in PAK1-null mutant of mice no inflammation occurs [264], (ii) ciclesonide (10 mg/kg/day) almost completely suppresses the PAK1-dependent growth of lung cancer (A541 cell line) in immune-deficient mice [265], and (iii) this hormone was recently presented to blocking PAK1-dependent replication and pathogenesis of COVID-19 infection [266].

Triptolide from Thunder God Vine and Its Water-Soluble Derivative

The herbal called "Triptolide from thunder god vine" was observed to inactivate RAC, thereby barring PAK1 [267, 259]. In 2010, triptolide was found to defeat virus production during dengue virus infection of the human lungs by obstructing the PAK1 signaling pathway [268]. But, its water-solubility is very poor. Thus, a group at the University of Minnesota headed by Gunda George boosted its water-solubility [269]. The resultant phosphatase-sensitive prodrug of triptolide called "Minnelide" is in clinical trials for cancers. Thus, both Triptolide and Minnelide could be possibly valuable for the treatment of coronavirus infection.

Ivermectin from Soil Bacterium (Streptomyces avermitilis)

In the 1975s, a precursor of Ivermectin (Avermectin) was identified from a soil bacterium by a group headed by Satoshi Omura, but it provokes side effects. To reducing its side effect, a Merck group directed by William Campbell, decreased it to create "Ivermectin" (dihydro-Avermectin), sharing the Nobel prize in 2015. It turned a medicine by Merck in 1981. It has been used to treat many types of parasite infestations including head lice, scabies, river blindness (onchocerciasis), among others. Three decades after this discovery, it was demonstrated by a Russian group to suppress the increase of cancers

as well, and ultimately, we discovered that its anti-cancer action is due to the inactivation of PAK1 [270]. So, it could possibly work as an alternative (and inexpensive) therapeutic to abolish the PAK1-dependent coronaviral infection as well. In fact, very recent studies proved that Ivermectin blocks the COVID-19 infection in animal experiments [271]. A curiosity is that the IC50 against COVID-19 is essentially the same as IC50 against the PAK1-dependent growth of cancer cells [272], which strongly suggests the PAK1-dependency of COVID-19 replication.

Artemisinin: Anti-Malaria from an Old Chinese Medical Herb

In 2015, Youyou Tu and colleagues discovered an anti-malaria compound called "Artemisinin" (AM). This substance was originally isolated from the plant Artemisia annua, a herb used in Chinese traditional medicine around the 1970s. Although the exact molecular mechanism about its anti-malaria and anti-viral action still persists unclear, the purpose is not the pathogens (Plasmodium falciparum or virus) themselves, but the host cells, most probably PAK1 or a component essential for both malaria and viral infection [273, 274], based on the next considerations: (i) the AM defeats both RAS (upstream of PAK1) and RAF (downstream of both RAS and PAK1) in T-cells [263, 276], and (ii) the dihydro derivative of AM suppresses the increase pancreatic cancer cells by upregulation of p21 (a CDK inhibitor) whose expression is suppressed by PAK1 [263, 273].

Extract of Chinese (Sichuan) Pepper (HuaJiao)

Chinese red peppercorns from Sichuan Province called "Hua Jiao" are among traditional spices adopted for the preparation of an old spicy Chinese cuisine called "Marbo-beancurd". In 2006, it was demonstrated that 70% ethanol or hot (above 45°C) water extract of Hua Jiao inhibits PAK1 with IC50 around 10 μg/mL, and thereby defeating cyclin D1 expression in both NF1-deficient triple-negative breast cancer (MDA-MB-231) and MPNST cell lines in which PAK1-is abnormally activated [277]. Thus, the drinking of "Hua Jiao" tea (extract) could be helpful in COVID-19 infection. However, its major PAK1-blocking component has not been chemically known as yet. So, further studies are necessary to investigate the positive evidence of "Hua Jiao" in COVID-19 treatment.

FK 228 (Istodax): Blocking HDAC-PAK1 Pathway

Fujisawa Pharm Group isolated FK228 from a soil bacterium in 1995. It well restrains the increase of RAS cancers such as pancreatic and colon cancers, which carry oncogenic mutant of Ki-RAS. A few years later it was discovered that it inhibits directly HDAC (histone deacetylase) with IC50 around 1 nM. In 2005, it was found that FK228 inactivates PAK1 in several cancer cells, including Tamoxiphen-resistant breast cancers and NF1-deficient MPNST (malignant peripheral nerve sheath tumor) [277]. In 2009, it was approved by FDA for the treatment of Cutaneous T-cell Lymphoma (CTCL). Thus, due to its property of inhibits HDAC and suppresses the increase of RAS, it could be useful for the therapy of COVID-19 infection as well.

Synthetic PAK1-Blockers

Ketorolac

"Toradol" is a racemic (1:1) mix of S- and R-forms of ketorolac. Since S-form directly inhibits COX-2, it has been used against pain. Nevertheless, a few years ago, R-form was observed to down-regulate RAC, thereby inactivating PAK1 [278, 279]. Thus, "Toradol" could be applied for the treatment of PAK1-dependent coronaviral infection. The resultant potent PAK1-blocker, called 1,2,3-triazolyl 295 ester of Ketorolac (15 K), suppresses both increase and metastasis of chemo-resistant human pancreatic cancer xenografts in mice with IC50 < 0.1 mg/kg/day, and causes no side effect even at 5 mg/kg/day

298 [280]. Thus, 15 K could be applied not only for pancreatic cancer therapy but also for therapy of infectious diseases caused by a coronavirus (COVID300 19) and many other dangerous viruses in the future.

Vitamin D3 and Its Derivative (MART-10)

The most generally known pharmacological action of Vitamin D3 is calcemic, i.e., stimulating the absorption of calcium into bone tissues. Nevertheless, researchers of Melbourne in the late 1980s, discovered that Vitamin D3 can suppress the increase of tumors in mice fed with a calcium-less diet [281]. However, the therapy with Vitamin D3 against cancers has never been successful. This clinical failure is due to the inactivation of Vitamin D3 by CYP24 in the human body.

Thus, a Japanese group in 2010 developed a derivative of Vitamin D3, called "MART-10", which is very resistant to CYP24 and definitely less calcemic [283]. The "MART-10" is 1000 times more powerful than Vitamin D3 against breast and pancreatic cancers [282]. A few years ago, a German group at Tuebingen University discovered that Vitamin D3 down-regulates RAC, inactivating PAK1 and leading to depolymerization of actin filaments [283]. Independently, MART-10 also induced the depolymerization of actin in cancer cells [284]. Moreover, CYP24 expression turned out to depend on the oncogenic RAS-PAK1-NF κB/ Ets signaling pathway [285]. Thus, probably, either "MART-10" alone or in combination with Vitamin D3 and a CYP24-resistant PAK1-blocker such as propolis could be possibly helpful for the treatment of coronaviral infection.

Pythochemicals and Natural Products Targeting Coronaviruses

Natural products can inhibit various steps in viral infection and replication, and many of them have broad-spectrum antiviral effects, the mechanisms of which have not been fully characterized. They also can function as immunomodulators, suppressing inflammatory reaction responsible for the major morbidity and mortality of SARS-CoV-2 infection. Phytochemicals, especially flavonoids, which are widely distributed in food plants and botanicals, have been shown to interfere with NLRP3 inflammasome signaling [286]. The respiratory distress syndrome associated with SARS coronaviruses develops in part due to viral activation of the NLRP3 inflammasome within activated macrophages and T helper-1 lymphocytes, which causes increased production of inflammatory cytokines [287]. Several flavonoids that interfere with activation of the NLRP3 inflammasome may modulate inflammatory response to SARS beta coronaviruses: luteolin [288], myricetin [289], apigenin [290], quercetin [291] kaempferol [292], baicalin [293], and wogonoside [294].

These flavonoids have been shown to be active against a wide variety of viruses, via multiple mechanisms [295, 296], and are available as nutraceutical supplements at a daily dose ranging from 100 mg to 500 mg. Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) (CAS number: 518−82-1) is an anthraquinone compound found in various Chinese herbs and is also produced by many species of fungi, including members of the genera Aspergillus, Pyrenochaeta, and Pestalotiopsis. Emodin has been shown to inhibit the interaction of SARS-CoV S protein with its receptor ACE2 in a dose-dependent manner [297]. Resveratrol (trans-3,5,4′-trihydroxystilbene) (CAS number: 501−36-0) is a stilbenoid and a natural polyphenol that is found in high concentrations in the skins of red wine grapes (Vitis vinifera), in red wine and in sprouted peanuts (Arachis hypogaea). Resveratrol has been demonstrated *in vitro* to inhibit MERS-CoV infection and to prolong cellular survival after virus infection. Further, expression of MERS-CoV nucleocapsid protein essential for virus replication as well as MERS-CoV- induced host

cell apoptosis are inhibited by resveratrol [298], suggesting that resveratrol may also be effective against SARS-CoV-2 infection.

Blood Purification Treatments

Blood purification treatments currently utilized in clinical practice are capable to eliminate some inflammatory factors. The purification system, which involves plasma replacement, adsorption, perfusion, blood/plasma filtration, and other procedures, can exclude some quantity of inflammatory factors, barring "cytokine storms", and decrease the damage from the body's inflammatory response. This treatment can be applied for critical patients in the early and middle phases of the disease. This artificial technology, which was led by Academician Li Lan-Juan, can reduce inflammatory factors on a huge scale. This technology has also been adopted to resist the cytokine storm of H7N9. The application of this treatment on COVID-19 has obtained certain efficiency [299]. Early renal replacement therapy appears to be an efficient method to control cytokine storm.

Inhibitors of Mononuclear Macrophage Recruitment and Function.

The autopsy of patients with COVID-19 revealed many inflammatory cell infiltration in the lungs of the deceased [300]. One treatment method that can be possibly efficient is to reduce the recruitment of mononuclear macrophages to the site of inflammation by small interfering RNA (siRNA)-mediated silencing of C-C chemokine receptor type 2 (CCR2) to increase the outcome of the disease [301, 302]. Toll-like receptor 7 (TLR7) agonists excite mononuclear macrophages to undergo a strong inflammatory response at the time of infection with single-stranded RNA (ssRNA) viruses such as HCoV. Hence, TLR7 antagonists may be able to mitigate the storm of inflammatory factors induced by SARS-CoV-2 infection.

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Table 1. Immune-based therapy under evaluation for treatment of COVID-19: clinical data to date. (*Last Updated: July 30, 2020*).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood-Derived Products			
COVID-19 Convalescent Plasma	• The FDA has provided recommendations for the use of COVID-19 convalescent plasma through EINDs for individual patients, traditional INDs, or expanded access INDs. The FDA has also approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information on that specific program and other trials evaluating convalescent plasma.	• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2. Thousands of U.S. patients have received convalescent plasma through clinical trials, expanded access treatment trials, and EIND applications. However, the standards and methods for screening donated plasma for SARS-CoV-2 binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may impact the product's efficacy. Clinical data are currently insufficient to evaluate the efficacy of convalescent plasma.	**For COVID-19:** • Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19: Investigators conducted an openlabel, randomized clinical trial of convalescent plasma *versus* SOC for patients with severe and life-threatening laboratory-confirmed COVID-19 in seven medical centers in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a reduction of 2 points on a 6-point disease severity scale. Only plasma units with SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer ≥ 1:640 were transfused. The median dose of ABO-compatible convalescent plasma was 200 mL. The time from symptom onset to randomization was 27 days in the treatment group and 30 days in the control group. Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned for 200 patients were enrolled. The convalescent plasma and control groups were well balanced by age (median age of 70 years vs. 69 years, respectively), but the control group had a higher proportion of men (65%) than the convalescent plasma group (52%). Baseline severity scores (45 patients had severe disease and 58 had life-threatening disease) and use of concomitant therapies were similar between the two groups. There was no significant difference between the groups in the primary outcome of time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; P = 0.26). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; OR 1.34; 95% CI, 0.98–1.83; P = 0.07). Among those with lifethreatening disease, 21% of the convalescent plasma recipients and 24% of the control patients improved by Day 28 (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; P = 0.75). There was no significant difference in 28-day mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; P = 0.30). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, P = 0.003 at 24 hours; 68% vs. 33%, P = 0.001 at 48 hours; and 87% vs. 38%, P <0.001 at 72 hours). Two transfusion-related events were reported, including 1 severe event; both events resolved with supportive care. The study's primary limitations were its open-label design and that, on average, administration of the convalescent plasma was approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect differences in clinical outcomes. • Preliminary Safety Analysis of the First Consecutive 5,000 Patients to Receive Open Label, COVID-19 Convalescent Plasma Through a National Expanded Access Program: The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program is an

			ongoing, open-label, nonrandomized protocol primarily designed to provide patients with severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives were to obtain safety data on the product. The protocol is sponsored by the Mayo Clinic and includes a diverse range of clinical sites. Plasma donors have documented COVID-19, with complete resolution of symptoms for at least 14 days prior to donation, and are either male, female without history of pregnancy, or female with history of pregnancy and negative HLA testing after the most recent pregnancy. SARS-CoV-2 antibody testing of donors is not mandated. ABO-compatible convalescent plasma is transfused preferentially, but in the absence of ABO-compatible plasma, patients may receive either Group A plasma or low anti-A titer Group O plasma, as available. The main safety outcomes for the safety analysis are SAEs including death; SAEs are reported at 4 hours and at 7 days after transfusion, or as they occur. The safety analysis describes the first 5,000 patients, enrolled between April 7 and May 3, 2020. Participants were adults with median age of 62 years, 63% male, and 81% had severe or life-threatening COVID-19. SAEs were reported in 36 patients (<1%) within 4 hours of transfusion; SAEs included 15 deaths, including 4 possibly or probably related to the convalescent plasma treatment. The 21 non-fatal SAEs included 7 TACO events, 11 TRALI events, and 3 severe allergic reactions. The overall 7-day mortality rate was 14.9%. In this study, COVID-19 convalescent plasma therapy was associated with a low rate (<1%) of serious transfusion-related events. The study design, which does not include a control arm, precludes an assessment of efficacy or ADE. • Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus Standard of Care *Versus* Standard of Care Without Convalescent Plasma: Not Peer Reviewed. This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the FDA's single patient EIND program while hospitalized at Mount Sinai Hospital in New York City during the period March 24 to April 8, 2020. Recipients were transfused with 2 units of ABOcompatible convalescent plasma from donors with a SARS-CoV-2 antispike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's EHR database. The control patients were hospitalized during the same period as the patients in the convalescent plasma group and had confirmed COVID-19 but did not receive convalescent plasma. They were matched 4:1 to the convalescent plasma recipients using propensity scores to correct for measured confounders. Convalescent plasma recipients had a mean age of 55 years and 64% were male. At the time of transfusion, 87% of the recipients required supplemental oxygen (noninvasive) and 10% were mechanically ventilated. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients (P = 0.17). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died (P = 0.04, log-rank test) and 72% of the transfused patients and 67% of the control patients had been discharged. Interpretation of the study results is limited by the lack of randomization and the potential for unmeasured patient selection bias. • Other smaller, uncontrolled case series describing clinical outcomes in patients with COVID-19 have been reported and also suggest that serious AEs are uncommon following COVID-10 convalescent plasma treatment.

SARS-CoV-2 Specific Immunoglobulins	• Not approved by the FDA	• Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response.	• No clinical data for COVID-19, SARS, or MERS
Non-SARS-CoV-2 Specific Intravenous Immunoglobulins	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy • Prophylaxis of various bacterial and viral infections	• Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors without confirmation of SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies. Furthermore, although IVIG contains other blood components that may have general immunomodulatory effects, it is unclear if these theoretical immunomodulatory effects will benefit patients with COVID-19.	**For COVID-19:** • Not Peer Reviewed. A retrospective, nonrandomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study found no difference in 28-day or 60-day mortality between 174 patients who were treated with IVIG and 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median stay of 24 days for IVIG group vs. 16 days for no IVIG group) and experienced longer duration of disease (median of 31 days for IVIG group vs. 23 days for no IVIG group). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). A subgroup analysis that was limited to the critically patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the no IVIG group. The IVIG group also had more patients with severe COVID-19 disease at study entry. Also, patients in both groups received many concomitant therapies for COVID-19.
Mesenchymal Stem Cells (MSCs)	• Not approved by the FDA	• Multipotent adult stem cells that are present in most human tissues including the umbilical cord • It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cellmediated inflammatory response induced by SARS-CoV-2. • MSCs lack the angiotensin-converting enzyme 2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.	**For COVID-19:** • A pilot study of IV MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common-type disease. Seven patients (1 with critical illness, 4 with severe illness, and 2 with common-type illness) received MSCs; 3 patients with severe illness received placebo. All 7 patients who received MSCs recovered. Among the 3 severely ill control patients, 1 died, 1 developed ARDS, and 1 remained stable with severe disease. **For Other Viruses:** • In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus SOC, and 44 patients received SOC only. In the MSC group, 3 patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to 5 patients in the MSC group. No safety concerns were identified.

Immunomodulators			
Corticosteroids			
Dexamethasone	FDA-Approved Indications: • Allergic states (e.g., severe or incapacitating asthma, dermatitis, drug HSRs) • Dermatologic diseases (e.g., bullous dermatitis, Stevens- Johnson syndrome) • Endocrine disorders (e.g., adrenocortical insufficiency) • Gastrointestinal diseases (e.g., ulcerative colitis) • Hematologic disorders (e.g., hemolytic anemia, idiopathic thrombocytopenia purpura, pure red cell aplasia) • Neoplastic diseases (e.g., palliative treatment of leukemia, lymphoma) • Nervous system disorders (e.g., multiple sclerosis, cerebral edema) • Ophthalmic diseases (e.g., temporal arteritis, uveitis) • Renal diseases (e.g., to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome) • Respiratory diseases (e.g., eosinophilic pneumonia) • Rheumatic disorders (e.g., ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)	• Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity. Glucocorticoid activity includes anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects. • Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19.	**For COVID-19:** • A preliminary, unpublished analysis from a large multicenter, randomized, open-label trial (RECOVERY) in hospitalized patients in the United Kingdom showed that those randomized to dexamethasone 6 mg daily (n = 2,104) had reduced mortality within 28 days of enrollment compared with those who received SOC (n = 4,321) (21.6% vs. 24.6%; RR 0.83; 95% CI, 0.74–0.92, P < 0.001). The survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.0% of participants in the dexamethasone group died within 28 days of enrollment compared with 40.7% of those in the control arm (RR 0.65; 95% CI, 0.51–0.82, P < 0.001). Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 21.5% in the dexamethasone arm died within 28 days of enrollment compared with 25.0% of those in the control arm (RR 0.80; 95% CI, 0.70–0.92, P = 0.002). No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.0% of dexamethasone participants died within 28 days of enrollment compared with 13.4% in the control arm (RR 1.22; 95% CI, 0.93–1.61, P = 0.14). Interpretation of these results is limited by several factors: full analysis of the trial is ongoing; the results of key secondary endpoints, potential adverse events, and efficacy in key subgroups have not been reported; there were not standardized or objective criteria for oxygen supplementation; and the age distribution of patients differed by respiratory status at the time of randomization (patients who received mechanical ventilation were more likely to be <70 years of age). • Small retrospective cohort studies and case series have yielded conflicting results regarding corticosteroids, with some suggesting benefits associated with short courses of corticosteroids and others showing potential harm. • Conversely, several publications from China including a meta-analysis of 15 studies (which included studies for treatment of COVID-19, SARS, or MERS)24 and a retrospective review of critically ill patients with COVID-19 suggest an increased risk of multi-organ dysfunction and no benefit in (to possibly increased risk of) mortality with use of corticosteroids.

Interferon Alfa and Interferon Beta			
Interferon Alfa	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States.	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types	**For COVID-19:** • An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or LPV/r. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants admitted within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (IFN beta-1b 8 million units SQ every other day for up to 7 days total, LPV/r, and ribavirin); those admitted ≥7 days after symptom onset (n = 51) were randomized to double therapy (LPV/r and ribavirin) because of concerns regarding potential inflammatory effects of IFN. All participants in the control group received LPV/r alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed SARS-CoV-2 infection who were hospitalized regardless of disease severity until they had two negative nasopharyngeal swabs. The median time to a negative SARS-CoV-2 PCR on a nasopharyngeal swab (the primary endpoint) was shorter for the combination group than for the control group (7 days vs. 12 days, P = 0.001). The combination group had more rapid clinical improvement as assessed by NEWS2 and SOFA score and a shorter hospital stay (9 days for combination group vs. 14.5 days for control group, P = 0.016). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset suggesting that IFN beta-1b with or without ribavirin was the critical component of the combination therapy. The study provides no information about the effect of IFN beta-1b administered >7 days after symptom onset. • Not Peer Reviewed. In a retrospective cohort study of 77 adults with moderate COVID-19 in China, those who used nebulized IFN alfa-2b with or without umifenovir (Arbidol) achieved viral clearance in the upper respiratory track faster and had lower systemic inflammation than those who used only umifenovir. However, results are difficult to interpret because participants in the IFN alfa-2b group were substantially younger than those in the umifenovir only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized formulation of IFN alfa-2b is not FDA approved for use in the United States.
Interferon Beta	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function) • Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV. • *In vitro* activity against MERS-CoV in lung cells.	

Interleukin-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease35 • IV formulation is not approved for use in the United States	• Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19:** • A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra to outcomes in 44 historical controls. The patients in both groups were admitted to the same hospital system in Paris, France. Cases were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed SARS-CoV-2 infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO2 ≤93% with ≥6L/min O2) or worsening hypoxia (SpO2 ≤93% with >3L/min O2 and a loss of ≥3% of O2 saturation on room air in the previous 24 hours). Historic controls were patients fulfilling the same eligibility criteria and admitted to the hospital from March 18 to March 24, 2020. SOC for both groups entailed use of HCQ, AZM, and parenteral beta-lactam antibiotics. Anakinra was dosed SQ as 100 mg twice daily for 72 hours, followed by anakinra 100 mg daily for 7 days. Clinical characteristics were similar between the groups, except that the case patients had a lower mean BMI (25.5 kg/m2 for cases vs. 29.0 kg/m2 for controls), longer duration of symptoms (8.4 days for cases vs. 6.2 days for controls), and a higher frequency of HCQ use (90% for cases vs. 61% for controls) and AZM use (49% for cases vs. 34% for controls). The primary outcome of either admission to the ICU for mechanical ventilation or death occurred among 13 cases (25%) and 32 controls (73%) (HR 0.22; 95% CI, 0.11–0.41). However, within the first 2 days of follow up, in the control group, 6 patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. CRP levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) in the anakinra group and 5 patients (11%) in the control group. The clinical implications of these findings are uncertain, due to limitations in the study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls. • A single-center case series reported on open-label use of anakinra in 9 hospitalized patients with COVID-19, presenting with 4–12 days of symptoms, requiring oxygen ≤6 L/min, and serum CRP ≥50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two patients also received HCQ plus AZM; the other 7 patients received no specific additional treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after the first dose of the drug. Good clinical outcomes were observed in the other eight patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients had elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group. • A single-center, retrospective, cohort study in Italy compared outcomes in 29 patients following open-label anakinra use with outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring noninvasive ventilation, and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival rate was 90% in the anakinra group and 56% in the control group (P = 0.009); however, the patients in the anakinra group were younger (median age of 62 years in anakinra group vs. 70 years in control group), and fewer patients had chronic kidney disease. High-dose anakinra was discontinued in 7 patients (24%) due to AEs (bacteremia in 4 patients, elevated liver enzymes in 3 patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of 7 patients received low-dose SQ anakinra (100 mg twice daily); however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.

Interleukin-6 Inhibitors **Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.**			
Sarilumab	• Rheumatoid arthritis	• Human recombinant monoclonal antibody • IL-6 receptor antagonist	**For COVID-19:** • Press Release: In a Phase 2/3 clinical trial (ClinicalTrials.gov Identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an IDMC recommended discontinuing the 200-mg arm and restricting future enrollment to critically patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). At the time of data analysis, of the 226 critical patients, the proportion of patients who had died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%). Comparing mortality alone, the proportion of patients who died was also lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among the patients with critical illness, the press release cited “negative trends” for most outcomes in patients with severe illness who received sarilumab.
Siltuximab	• Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist	**For COVID-19:** • Not Peer Reviewed. In a single-center observational study of 21 patients with COVID-19 who developed pneumonia/ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (7 of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (9 of 21 patients) or worsening condition (5 of 21 patients). Among the 5 patients with worsening condition, there was 1 death and 1 cerebrovascular event (median follow-up of 8 days).
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	**For COVID-19:** • Press Release: Early results were reported for the CORIMUNO-TOCI trial (ClinicalTrials.gov Identifier NCT04331808), an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129) at 7 sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (n = 65) or SOC alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • 63 hospitalized adult patients were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg); within 24 hours, a second dose was administered to 52 of the 63 patients. Following tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The PaO2/FiO2 ratio increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were

				reported. Overall mortality was 11% (7 deaths among the 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association of reduced mortality with earlier use of tocilizumab, but provide no details regarding a comparison group or specify an a-priori comparison, which limits interpretation of this result. • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation. At study entry, among the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and 4 had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (2 required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 µg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, 3 patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group. • Additional data supporting the use of tocilizumab for COVID-19 include a small retrospective cohort study, a case series, and a case-control study
Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors				
Acalabrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL)	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm	**For COVID-19:** • Data regarding acalabrutinib are limited to a retrospective case series in 19 patients with severe COVID-19. However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.	
Ibrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL) • Marginal zone lymphoma (MZL) • Waldenström macroglobulinemia (WM) • Chronic graft-*versus*-host disease (cGVHD) in stem cell transplant recipients	• First-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm	**For COVID-19:** • Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of 6 patient with COVID-19 who were receiving ibrutinib for a condition other than COVID-19. However, evaluation of the data for any clinical benefit is limited by the study's small sample size and lack of control group.	

Zanubrutinib	• Mantle cell lymphoma (MCL)	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm	• No clinical data for COVID-19, SARS, or MERS
Baricitinib	• Rheumatoid arthritis	• JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3 • Theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells. • Dose-dependent inhibition of IL-6 induced STAT3 phosphorylation	**For COVID-19:** • Not Peer Reviewed. A small, nonrandomized study of 12 patients with moderate COVID-19 pneumonia compared therapy with baricitinib and LPV/r with SOC alone (i.e., combination LPV/r and HCQ).58 Baricitinib and LPV/r therapy demonstrated a statistically significant time to improvement in clinical and respiratory symptoms and reduction in measured CRP.
Ruxolitinib	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-*versus*host disease	• JAK inhibitor selective for JAK1 and JAK2 • Theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells • Inhibition of IL-6 via JAK1/JAK2 pathway inhibition	**For COVID-19:** • A small, prospective, single-blind randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg PO twice daily (n = 20) to placebo (vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; P = 0.15), defined as a 2-point improvement on a 7-category ordinal scale or hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; P = 0.94). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on CT scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; P = 0.05), and a shorter time to recovery from initial lymphopenia when present (5 days for ruxolitinib vs. 8 days for placebo; P = 0.03). The use of ruxolitinib was not associated with an increased risk of AEs or mortality (no deaths in the ruxolitinib group vs. 3 deaths [14% of patients] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in time to viral clearance among patients who had detectable viral loads at randomization to ruxolitinib (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (by 70% of patients) of antivirals and steroids. • A small retrospective single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (median 9 days).

Tofacitinib	• Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis	• JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2 • Blocks signaling from gammachain cytokines (IL-2, IL-4) and gp 130 proteins (IL-6, IL-11, IFNs) • Shown to decrease levels of IL-6 in rheumatoid arthritis	• No clinical data for COVID-19, SARS, or MERS

Key: AAK1 = Adaptor-associated kinase 1; ADE = antibody-dependent enhancement; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CRP = C-reactive protein; CI = confidence interval; CT = computerized tomography; EHR = electronic health record; EIND = Emergency Investigational New Drug Application; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; HR = hazard ratio; HSR = hypersensitivity reaction; ICU = intensive care unit; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IND = Investigational New Drug application; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; MSC = mesenchymal stem cells; NEWS2 = National Early Warning Score 2; OR = odds ratio; PCR = polymerase chain reaction; PI = protease inhibitor; RR = age-adjusted rate ratio; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SQ = subcutaneous; STAT3 = signal transducer and activator of transcription 3; TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury.

Credit/Source: NIAID-RML [15]. Available at: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/table-2a-potential-antiviral-agents-clinical-data/. Information presented in this table may include data from pre-prints or non-peer reviewed articles.

Table 2. Potential antiviral agents under evaluation for treatment of COVID-19: clinical data to date. (*Last updated July 30, 2020*).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Azithromycin **Note:** Most studies of COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections	• Induction of IFN-stimulated genes, attenuating viral replication • Enhanced neutrophil activation • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells	AZM has primarily been studied for the treatment of COVID-19 in combination with HCQ. The RECOVERY trial includes an AZM monotherapy arm, which is currently enrolling. • Please see the description of the combination therapy study results in the Hydroxychloroquine Plus Azithromycin section below and in Hydroxychloroquine Plus Azithromycin.
Chloroquine	• Malaria • Extra-intestinal amebiasis	• Increases endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes • Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with binding of SARS-CoV to the cell receptor • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome • Immunomodulatory effects	**High-Dose vs. Low-Dose CQ:** • A randomized, double-blind, Phase 2b study compared 2 different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) vs. CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected cases of severe COVID-19 (respiratory rate >24 breaths/min, heart rate >125 bpm, oxygen saturation <90%, and/or shock). All patients received ceftriaxone plus AZM; 89.6% of patients received oseltamivir. Of note, both AZM and oseltamivir can increase the QTc interval. • The primary outcome for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was sufficient to show a reduction in mortality by 50% with high-dose CQ. The study was stopped by the study's DSMB after 81 patients were enrolled. *Results:* • 41 and 40 patients were randomized into the high-dose and lowdose CQ arms, respectively. • The overall fatality rate was 27.2%. • Mortality by Day 13 was higher in the high-dose arm than in the lowdose arm (death occurred in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%], respectively; P = 0.03). This difference was no longer significant when controlled by age (OR 2.8; 95% CI, 0.9–8.5). • Overall, QTcF >500 ms occurred more frequently in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients). Among those with confirmed COVID-19, QTcF >500 ms was also more frequent in the high-dose arm (24.1% of patients) than in the low-dose arm (3.6% of patients). • 2 patients in the high-dose arm experienced ventricular tachycardia before death. *Limitations:* • More older patients and more patients with history of heart disease were randomized to the high-dose arm than to the low-dose arm. *Interpretation:* • Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose CQ (600 mg twice daily) is administered in combination with AZM and oseltamivir.

			CQ vs. LPV/r: • In a small, randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to receive oral CQ 500 mg twice daily or LPV/r 400 mg/100 mg twice daily for 10 days. Patients with a history of heart disease (chronic disease and a history of arrhythmia), or kidney, liver, or hematologic diseases were excluded from participation. The primary study outcome was a negative SARS-CoV-2 PCR test result at Days 10 and 14. Secondary outcomes included improvement of lung CT scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety (which was determined by evaluating study drug-related AEs). *Results:* • Ten patients received CQ and 12 patients received LPV/r. At baseline, patients had good SpO2 levels (97% to 98%). • Compared to the LPV/r-treated patients, the CQ-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days, P < 0.001). • Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years; P = 0.09). Few patients had comorbidities. • At Day 10, 90% of the CQ-treated patients and 75% of the LPV/rtreated patients had a negative SARS-CoV-2 PCR test result. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 91.2%, respectively. • At Day 10, 20% of the CQ-treated patients and 8.3% of the LPV/r-treated patients had CT scan improvement. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 75%, respectively. • At Day 14, 100% of the CQ-treated patients and 50% of the LPV/rtreated patients were discharged from the hospital. • The risk ratios of these outcome data cross 1, and the results were not statistically significant. • Both drugs were generally well tolerated. *Limitations:* • The trial sample size was very small, and the participants were fairly young. • The CQ-treated patients were younger and had fewer symptoms prior to treatment initiation; these variables could have affected the study protocol-defined outcomes. • Patients who had chronic comorbidities and who were critically ill were excluded from the study. *Interpretation:* • In this small randomized controlled trial, CQ and LPV/r showed similar efficacy in treating COVID-19.
Hydroxy-chloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis	• Increases the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes4 • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome • Immunomodulatory effects	**New York Department of Health Study on HCQ With or Without AZM:** • A retrospective, multicenter, observational study in New York evaluated the use of HCQ with and without AZM in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into 4 treatment groups: HCQ plus AZM, HCQ alone, AZM alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an ECG. *Results:* • Patients in the 3 treatment groups had more severe disease at baseline than those who received neither drug.

• In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.
• Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).
Limitations:
• Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.
Interpretation:
• Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of inhospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.

Observational Study of HCQ at a Large Medical Center in New York City:
• This observational study evaluated 1,376 consecutive adults with COVID-19 who were admitted to a large New York City hospital (after excluding 70 patients who died or who were transferred within 24 hours after presenting to the emergency department). The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received HCQ at baseline or during follow-up. Patients who received HCQ were prescribed a twice-daily dose of HCQ 600 mg on the first day and 400 mg daily for 4 additional days; this was based on the clinical guidance of the hospital.
Results:
• 811 patients (58.5%) received HCQ and 565 (41.1%) did not.
• Patients who received HCQ were older and more likely to have hypertension (49.1% vs. 6.7%) and to be on systemic steroids (26.6% vs. 10.1%) than those who did not receive HCQ.
• Patients who received HCQ were more likely to receive concomitant AZM (59.9% vs. 22.5%) and/or other antibiotics (74.5% vs. 54.0%) than those who did not receive HCQ.
• Patients who received HCQ had higher levels of inflammatory markers.
• HCQ-treated patients had more severe hypoxia, with a lower PaO2/FiO2 ratio at baseline than patients who did not receive HCQ (median of 233 mm Hg vs. 360 mm Hg).
• Most patients (85.9%) received HCQ within 48 hours of presentation.
• Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32).
• There was also no association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).
Limitations:
• Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.
Interpretation:
• The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Retrospective Observational Cohort from the United States Veterans Health Administration

This study has not been peer reviewed

• An observational, retrospective cohort study analyzed data from patients with confirmed COVID-19 who were hospitalized at the United States Veterans Health Administration medical centers between March 9–April 11, 2020. Patients were categorized as having received either HCQ, HCQ plus AZM, or no HCQ. Doses and duration of HCQ or AZM use were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic data, comorbidity data, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if BMI, vital signs, and discharge disposition were noted in their medical records.

Results:

• 368 patients were eligible for analysis. These patients were categorized into 3 treatment groups: HCQ (n = 97), HCQ plus AZM (n = 113), or no HCQ (n = 158). The median ages for the patients in each group were 70, 68, and 69 years, respectively. All patients were male.

• 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation.

• No difference was observed between the groups in the risk of mechanical ventilation.

• The risk of death from any cause was higher in the HCQ group than in the no HCQ group (adjusted HR 2.61; 95% CI, 1.10–6.17; P = 0.03). The no HCQ group and the HCQ plus AZM group had similar risks of death from any cause (adjusted HR 1.14; 95% CI, 0.56–2.32, P = 0.72).

• There was no between-group difference in the risk of death after ventilation.

Limitations:

• The patient population was entirely male.

• The dose and duration of administration for HCQ and AZM were not included in the report. Patients were included if they received a single dose of either or both drugs.

• Propensity score adjustment was used to account for differences between the groups; however, the possibility of residual confounding cannot be excluded, as patients who were more ill may have been more likely to receive HCQ.

• No imaging data were presented; the severity of chest X-ray findings could predict worse outcomes.

• The use of other antiviral or immunomodulatory agents were not reported.

• The reason for the high mortality rate among patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild or moderate disease at admission.

Interpretation:

• This study showed no beneficial effect of HCQ plus AZM for the treatment of COVID-19 and a possible association between the use of HCQ and an increased risk of mortality; however, residual confounding may have affected the study results.

Randomized, Controlled Trial of HCQ vs. SOC for Mild or Moderate COVID-19:

• This multicenter, randomized, open-label trial compared HCQ 1,200 mg once daily for 3 days followed by HCQ 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild or moderate COVID-19 [99% of the patients] and 3 weeks for 2 patients with severe disease) and SOC.

• The primary outcome was a negative PCR test result within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO2 >94% on room air, resolution of respiratory symptoms), improvement in markers of inflammation (including CRP levels), and improvement of lung lesions on a chest X-ray within 28 days.

Results:

• 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset.

• The HCQ arm and the SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants, respectively) and similar times to negative PCR conversion (median of 8 days vs. 7 days, respectively).

• There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.

• AEs occurred in 30% of the participants in the HCQ arm (most commonly diarrhea) and in 9% of the participants in the SOC arm.

Limitations:

• It is unclear how the overall rate of symptom alleviation was calculated.

• The duration of HCQ use (2 weeks) was longer than in most other observational cohort studies or clinical trials for the treatment of COVID-19.

• The study did not reach the target sample size.

Interpretation:

• This study demonstrated no difference in viral clearance between HCQ and SOC.

Observational Cohort of HCQ vs. No HCQ:

• This observational, retrospective cohort study analyzed data for adult patients who were hospitalized for COVID-19 pneumonia at 4 French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18–80 years were eligible if they had PCR-confirmed SARS-CoV-2 infection and required oxygen by mask or nasal cannula. Exclusion criteria included HCQ initiation before hospitalization, receipt of another experimental COVID-19 treatment within 48 hours, organ failure that required immediate admission to the ICU or continuous care unit, admission with ARDS that required noninvasive ventilation with continuous positive airway pressure or mechanical ventilation, discharge from the ICU to standard care, or if a decision was made to limit or stop active treatments prescribed at admission. Patients in 1 treatment arm received a daily dose of HCQ 600 mg within 48 hours of admission; patients in the other arm did not receive HCQ during the same period. The decision to use HCQ to treat a patient was based on local medical consensus and prescriber opinion and was reportedly independent of patient characteristics. Patients were followed from baseline until death, loss to follow-up, or the end of the follow-up period on April 24, 2020. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization.

Results: • Of the 181 patients who were eligible for the analysis, 84 participants received HCQ within 48 hours, 8 received HCQ beyond 48 hours, and 89 did not receive HCQ. • Comorbidities were less common in the HCQ group; overall initial COVID-19 severity was well balanced across the treatment arms. • In the HCQ group, 18% of the patients received concomitant AZM and 52% of the patients received amoxicillin/clavulanic acid. • In the inverse probability of treatment weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ group (76% of participants) and the non-HCQ group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival rate and survival rate without ARDS at Day 21. • Among the 84 patients who received HCQ within 48 hours, 8 patients (10%) experienced ECG changes that required treatment discontinuation at a median of 4 days from the start of dosing, including 7 patients with a QTc that prolonged >60 ms and 1 patient with new onset, first-degree AV block. None of these patients received AZM. *Limitations:* • This was a retrospective, nonrandomized study. *Interpretation:* • In this retrospective study, there was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.			
A Case Series of HCQ vs. Control: • In a case series from France, 26 hospitalized adults with either asymptomatic SARS-CoV-2 infection or upper or lower respiratory tract infection received HCQ 200 mg 3 times daily for 10 days. These patients were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic). *Results:* • 6 patients in the HCQ group were excluded from the analysis for the following reasons: • 1 patient died, • 3 patients were transferred to the ICU, • 1 patient stopped the study drug due to nausea, and • 1 patient withdrew from the study. • 6 patients also received AZM. • By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and 2 of 16 controls (12.5%). • Among the HCQ patients, 8 of 14 (57.1%) who received only HCQ and 6 of 6 (100%) who received HCQ and AZM had negative NP PCRs by Day 6. • Clinical outcomes were not reported for all patients. *Limitations:* • The sample size of the series is small. • The criteria for enrollment of cases and controls is unclear. • Asymptomatic individuals were enrolled. • Exclusion of 6 HCQ-treated patients includes 1 death and 3 ICU transfers. • No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown. • The reason for the addition of AZM for some patients is unclear. *Interpretation:* • Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of HCQ with or without AZM.		

Hydroxy-chloroquine Plus Azithromycin	See the Azithromycin and Hydroxychloroquine sections above.	See the Azithromycin and Hydroxychloroquine sections above.	**Case Series of HCQ Plus AZM:** • In a case series of 80 hospitalized patients with COVID-19 (including 6 patients from a previous study),14 patients were treated with HCQ 200 mg 3 times daily for 10 days plus AZM 500 mg once daily for 1 day followed by AZM 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. The outcomes that were evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, SARS-CoV-2 level as determined by PCR, SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward. *Clinical Results:* • 1 patient died (1.2%), 3 required ICU transfer (3.8%), and 12 required oxygen therapy (15%). • 65 patients (81.2%) were discharged to their homes or transferred to other units for continuing treatment; 14 patients (17.4%) remained hospitalized at the time the study results were published. *Laboratory Results:* • SARS-CoV-2 NP PCR was negative in 83% of patients by Day 7 and in 93% of patients by Day 8. • In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples. *Limitations:* • The trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment. • The trial lacked complete or longer-term follow-up. *Interpretation:* • The multiple issues with trial design and the lack of a control group limit the usefulness of this study for informing recommendations. **Small Prospective Case Series of HCQ Plus AZM:** • A prospective case series from France assessed 11 consecutive hospitalized patients with COVID-19. *Results:* • 8 of the 11 patients had significant comorbid conditions: obesity (n = 2), solid cancer (n = 3), hematological cancer (n = 2), and HIV infection (n = 1). • 10 of 11 patients were receiving supplemental oxygen at treatment initiation. • All patients were treated with HCQ 600 mg once daily for 10 days and AZM 500 mg once daily for 1 day followed by AZM 250 mg once daily for 4 days. • Within 5 days, the condition of 3 patients worsened, including 1 patient who died and 2 patients who were transferred to the ICU. • HCQ was discontinued in 1 patient due to QTc prolongation. • Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in 8 of 10 patients. *Limitations:* • This is a case series that included a small number of patients. *Interpretation:* • In this small case series, most patients who received HCQ plus AZM did not have rapid viral clearance.

			Case Series of Changes in QTc Interval in Patients Who Received HCQ Plus AZM: • A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days) and AZM (500 mg once daily for 5 days). *Results:* • 84 patients were enrolled; 74% were male, with a mean age of 63 ± 15 years. 65% had HTN, mean serum creatinine was 1.4 mg/dL at baseline, 13% required vasopressors, and 11% had CAD. • Some participants were receiving concomitant drugs that had the potential to prolong the QTc interval; 11% of participants were receiving neuropsychiatric drugs and 8% of participants were receiving levofloxacin, LPV/r, or tacrolimus. • 4 patients died, without arrhythmia. • The mean baseline QTc was 435 ± 24 ms and the mean maximum QTc was 463 ± 32 ms. • The mean time to maximum QTc was 3.6 ± 1.6 days. ECG follow-up was done for a mean of 4.3 days. • 9 patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively. *Limitations:* • This was a descriptive case series. *Interpretation:* • This case series demonstrated that HCQ plus AZM can prolong QTc and that the use of this combination warrants careful monitoring.
HIV Protease Inhibitors Note: LPV/r and DRV/c have been studied in patients with COVID-19	HIV infection	• No data on *in vitro* activity of LPV/r against SARS-CoV-2 • Possible inhibition of SARS-CoV-2 protease 3CLpro • *In vitro* data does not support the use of DRV/c for the treatment of COVID-19	**LPV/r Pharmacokinetics in Patients With COVID-19:** • In a case series, 8 patients with COVID-19 were treated with LPV/r 400 mg/100 mg orally twice daily and had plasma trough levels of LPV drawn and assayed by liquid chromatography-tandem mass spectrometry. *Results:* • The median plasma LPV concentration was 13.6 µg/mL. • After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the *in vitro* EC50 for SARS-CoV-2. *Limitations:* • Only the trough levels of LPV were quantified. • No data are available on effective LPV concentrations for SARS-CoV-2 *in vivo*. *Interpretation:* • The plasma drug concentrations that were achieved using typical doses of LPV/r are far below the levels that may be needed to inhibit SARS-CoV-2. **Randomized Controlled Trial of LPV/r vs. SOC:** • In a clinical trial that randomized 199 patients to receive LPV/r 400 mg/100 mg PO twice daily for 14 days or SOC, patients who were randomized to the LPV/r arm did not have a shorter time to clinical improvement. *Results:* • There was a lower, but not statistically significant, mortality rate for the LPV/r group (19.2%) than for the SOC group (25.0%), and a shorter ICU stay for those in the LPV/r group than those in the SOC group (6 days vs. 11 days; difference of -5 days; 95% CI, -9 to 0 days).

		• The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the LPV/r and SOC arms. • Nausea, vomiting, and diarrhea were all more frequent in the LPV/rtreated group. • The study was powered only to show a fairly large effect. *Limitations:* • The study was not blinded, which may have affected the assessments of clinical improvement. • The study was underpowered to show small effects. *Interpretation:* • A moderate-sized, randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC.
		LPV/r Plus IFN Beta-1b Plus Ribavirin for COVID-19: • Also see Interferons for a description of this trial and its results. • An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included IFN beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus LPV/r 400 mg/100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of LPV/r 400 mg/100 mg every 12 hours alone. • In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, IFN beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only 1 participant was mechanically ventilated. *Results:* • Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group. *Limitations:* • Participants in both arms received LPV/r, so it is impossible to determine whether LPV/r contributed to the observed treatment effects. However, the possibility that LPV/r may have contributed to the effectiveness of the combination therapy also cannot be ruled out. • The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset. • Most participants in this study had mild illness, and only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States. *Interpretation:* • This study neither supports nor refutes the use of LPV/r with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.
		LPV/r vs. Umifenovir vs. SOC • In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to receive LPV/r, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received SOC.

			Results (Comparison of LPV/r to SOC): • The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving LPV/r (mean 9 days [SD ± 5.0]) and for those receiving SOC (mean 9.3 days [SD ± 5.2]). • Progression to severe illness occurred among 6 patients (18%) in the LPV/r arm and 2 patients (12%) who received SOC. • 2 patients became critically ill; both were randomized to receive LPV/r. *Limitations:* • The trial had a small sample size. • The study was not blinded. • The effectiveness of umifenovir in treating COVID-19 is unknown. Interpretation: • The small sample size of this trial limits its usefulness. **LPV/r vs. CQ:** • A small randomized study in China compared LPV/r to CQ. Please refer to the Chloroquine section above for the study description.
Remdesivir (GS-5734)	• Not approved by FDA	• Binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription • Has demonstrated *in vitro* activity against SARS-CoV-24 • In a rhesus macaque model of SARS-CoV-2 infection, RDV treatment was initiated soon after inoculation; RDVtreated animals had lower lung virus levels and less lung damage than the control animals.	**Multinational Randomized Controlled Trial of RDV vs. Placebo in Hospitalized Patients:** • ACTT is an NIH-sponsored, multinational, randomized, doubleblind placebo-controlled trial in hospitalized adults with COVID-19. Participants were randomized 1:1 to receive IV RDV or placebo for 10 days. The primary study endpoint was time to clinical recovery, which was defined as either discharge from the hospital or hospitalization for infection control purposes only. Severity of illness at baseline and at Day 15 was assessed using an ordinal scale: 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, no active medical problems 4. Hospitalized, not on oxygen 5. Hospitalized, on oxygen 6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation 7. Hospitalized, on mechanical ventilation or ECMO 8. Death *Study Population:* • The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection. Patients were enrolled if they met at least 1 of the following conditions: • The patient had pulmonary infiltrates, as determined by radiographic imaging, • SpO2 was ≤94% on room air, • The patient required supplemental oxygen, • The patient was on mechanical ventilation, or • The patient was on ECMO. • The study excluded individuals who had ALT or AST levels >5 times the ULN, those who had an eGFR <30 mL/min, and those who were pregnant or breastfeeding. *Preliminary Results:* • Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the RDV group; n = 521 for the placebo group). • The mean age was 58.9 years; 64.3% of participants were male, 53.2% were white, and 79.8% were enrolled in North America. • 52.1% of participants had 2 or more comorbidities; 37% were obese (mean BMI 30.6 kg/m2) • The median time from symptom onset to randomization was 9 days (IQR 6–12 days). • At the time of the preliminary analysis, 391 RDV recipients and 340 placebo recipients had completed the study through Day 29, recovered, or died.

			• 8 RDV recipients and 9 placebo recipients terminated the study prior to Day 29. • At the time of this preliminary analysis, 132 RDV recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit. • RDV significantly reduced time to recovery compared to placebo (median time to recovery 11 days vs. 15 days, respectively; recovery rate ratio 1.32; 95% CI, 1.12–1.55; P < 0.001). • Clinical improvement based on the ordinal scale was significantly higher in patients who received RDV than in those who received placebo at Day 15 (OR 1.50; 95% CI, 1.18–1.91, P < 0.001). • The benefit of RDV on reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 421; recovery rate ratio 1.47; 95% CI, 1.17–1.84). In a post-hoc analysis of 14-day survival, remdesivir appeared to confer a survival benefit in this subgroup (HR 0.22; 95% CI, 0.08–0.58). • In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 197), there was no observed difference between the remdesivir and placebo groups in time to recovery (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In a post-hoc analysis of 14-day survival, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38). • Among the patients who were on mechanical ventilation or ECMO at enrollment (ordinal scale 7, n = 272), there was no observed difference between the RDV and placebo groups in time to recovery (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In a post-hoc analysis of 14-day survival, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92). • Among the patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the RDV and placebo groups (n = 119; recovery rate ratio 1.09; 95% CI, 0.73–1.62). Mild to moderate disease was defined as SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen. • The mortality estimate by Day 14 was lower in the RDV arm than in the placebo arm (7.1% vs. 11.9%, respectively), but the difference was not statistically significant (HR 0.70; 95% CI, 0.47–1.04). • The use of RDV was associated with shorter time to recovery regardless of the duration of symptoms prior to randomization (≤10 days vs. >10 days). • The percentages of participants with serious AEs were similar in the RDV and placebo groups (21.1% vs. 27.0%, respectively). • Transaminase elevations occurred in 4.1% of RDV recipients and 5.9% of placebo recipients. *Limitations:* • At the time of publication, the full dataset was not available for analysis. *Interpretation:* • In patients with severe COVID-19, RDV reduced the time to clinical recovery. The benefit of RDV was most apparent in hospitalized patients who required only supplemental oxygen. There was no observed benefit of RDV in those who were on high-flow oxygen, noninvasive ventilation, mechanically ventilation or ECMO, but the study was not powered to detect differences in subgroups. There was no observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Multinational Randomized Trial of Different Durations of RDV Treatment in Hospitalized Patients: • This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV RDV. The primary study endpoint was clinical status at Day 14, which was assessed using a 7-point ordinal scale: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices 4. Hospitalized, requiring low-flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons 6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for RDV administration) 7. Not hospitalized *Study Population:* • The study enrolled hospitalized patients aged ≥12 years with RT-PCRconfirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates. Patients in this study had either SpO2 ≤94% on room air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated CrCl <50 mL/min. Patients were also excluded if they had received an agent with putative anti-SARS-CoV-2 activity within 24 hours of starting treatment in the trial. *Results:* • Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of RDV treatment. • In the 5-day group, the median age was 61 years; 60% of participants were male, and 71% were white. In the 10-day group, the median age was 62 years; 68% of participants were male, and 70% were white. The frequency of coexisting conditions was similar in both groups. • The median time from symptom onset to first dose of RDV was 8 days in the 5-day group and 9 days in the 10-day group. The median duration of hospitalization before the first RDV dose was 2 days in both groups. • At baseline, patients in the 10-day group had worse clinical status (based on the ordinal scale distribution) than those in the 5-day group (P = 0.02). • A few patients were on mechanical ventilation: 4 patients (2%) were assigned to the 5-day group, and 9 patients (5%) were assigned to the 10-day group. Although mechanical ventilation was an exclusion criterion for enrollment, some patients were intubated between screening and treatment initiation; others were protocol deviations. • 172 participants (86%) in the 5-day group completed a median of 5 days of treatment, and 86 (44%) in the 10-day group completed a median 9 days of treatment. • 65% of patients in the 5-day group and 54% of those in the 10-day group had a 2-point improvement in clinical status on the ordinal scale. • After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups (P = 0.14) • The time to clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days, respectively).			

			• The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10 days) and 10-day group (8 days; IQR 5–10 days). • By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 patients (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 patients (11%) had died. • Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%); 4% of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs. *Limitations:* • This was an open-label trial without a placebo control group, so the clinical benefit of RDV could not be assessed. • There were baseline imbalances in the clinical statuses of participants in the 5-day and 10-day groups. At the start of the study, more patients in the 10-day group than in the 5-day group were receiving noninvasive ventilation or high-flow oxygen (30% vs. 24%, respectively), and fewer patients in the 10-day group than in the 5-day group were not receiving supplemental oxygen (11% vs. 17%, respectively). *Interpretation:* • In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had similar clinical benefit. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of RDV treatment for critically ill patients is still unclear.
			Randomized Controlled Trial of RDV vs. Placebo for Severe COVID-19 in China: • This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China. Patients were randomized 2:1 to receive IV RDV or normal saline placebo for 10 days. Concomitant use of LPV/r, corticosteroids, and interferons was allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients. • The study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days, whose O2 saturation was ≤94% on room air or whose PaO2/FiO2 was <300 mmHg, and who had radiographically confirmed pneumonia. *Results:* • Between February 6–March 12, 2020, 237 hospitalized patients were enrolled and randomized to receive RDV (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China. • The participants' median age was 65 years; 56% of the participants in the RDV arm and 65% in the placebo arm were male. • There were more patients with HTN, DM, or CAD in the RDV arm than in the placebo arm. • At Day 1, 83% of the patients required supplemental oxygen by nasal cannula or mask; only 1 patient required mechanical ventilation or ECMO.

			• The median time from symptom onset to randomization was 9 days in the RDV group and 10 days in the placebo group. • 65% of participants in the RDV group and 68% of participants in the placebo group received corticosteroids. • 28% of participants in the RDV group and 29% of participants in the placebo group received LPV/r. • 29% of participants in the RDV arm and 38% of participants in the placebo arm received IFN alfa-2b. *Study Endpoints:* • There was no difference in the time to clinical improvement between the RDV and placebo groups (a median of 21 days vs. 23 days, respectively; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen in the RDV arm than in the placebo arm (median of 18 days vs. 23 days, respectively; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • The 28-day mortality rate was similar for the 2 study arms (14% of participants in the RDV arm vs. 13% in the placebo arm). • There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the 2 groups. • The number of participants who experienced AEs was similar between the 2 groups (66% of participants in the RDV arm vs. 64% in the placebo arm). • More participants in the RDV arm discontinued therapy due to AEs (12% of participants in the RDV arm vs. 5% in the placebo arm). *Limitations:* • The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes. • The use of concomitant medications (i.e., corticosteroids, LPV/r, IFNs) may have obscured the effects of RDV. *Interpretation:* • There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between RDV-treated and placebo-treated patients. **Uncontrolled Case Series from RDV Compassionate Use Program** • In an uncontrolled case series of 53 hospitalized patients with COVID-19, most patients needed less oxygen support after receiving compassionate use RDV. There was no comparison group, however, so it is not possible to assess whether the improvement was the result of using RDV.

Key: 3CLpro = 3-chymotrypsin-like protease; ACE2 = angiotensin-converting enzyme 2; ACTT = Adaptive COVID-19 Treatment Trial; AE = adverse effect or adverse event; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CQ = chloroquine; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; DM = diabetes mellitus; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; EC50 = half-maximal effective concentration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; IFN = interferon; IL = interleukin; IQR = interquartile range; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NIH = National Institutes of Health; NP = nasopharyngeal; OR = odds ratio; PCR = polymerase chain reaction; PO = orally; QTcF = corrected QT interval by Fredericia; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; STI = sexually transmitted infection; ULN = upper limit of normal.
Credit/Source: NIAID-RML [15]. Available at: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/table-2a-potential-antiviral-agents-clinical-data/. Information presented in this table may include data from pre-prints or non-peer reviewed articles.

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