Onwudiwe OA, Weli H, Shaanu TA, Akata NM, Ebong IL. Pharmacological treatment of COVID-19: an update. *Journal of Global Health Reports*. 2020;4:e2020090. doi:10.29392/001c.17372

Reports

# Pharmacological treatment of COVID-19: an update

Oyiyechukwu A Onwudiwe[1], Homayemem Weli[2], Toluwanimi A Shaanu[3], Nkechi M Akata[4], Imoh L Ebong[5]

[1] College of Medicine, University of Lagos, Lagos, Nigeria, [2] Department of Pediatrics, Washington University School of Medicine, St Louis, Missouri, USA, [3] College of Medicine, Lagos State University, Lagos, Nigeria, [4] College of Medicine, University of Nigeria Nsukka, Nigeria, [5] School of Medicine and Dentistry, University of Ghana, Accra, Ghana

Keywords: therapy, sars-cov-2, covid-19, treatment, pharmacological

https://doi.org/10.29392/001c.17372

Journal of Global Health Reports

Vol. 4, 2020

## Background

The ongoing coronavirus disease-19 (COVID-19) pandemic, caused by the novel coronavirus 2 (SARS-CoV-2) has triggered a worldwide search for medications addressing the morbidity and mortality associated with it. Various medications have been proposed and applied to control COVID-19 based on previous experiences with other viral infections. Some of these have been shown to be harmful or lack efficacy. This review discusses the medications that have been repurposed for SARS-CoV-2, experimental medications undergoing clinical trials, as well as the regional variations in COVID-19 treatments.

## Methods

A literature search was conducted to cover the period of January 2020 to September 2020 using the keywords "medications, treatment, therapeutics, pharmacological management for COVID-19" in various combinations as search strings. PubMed, LitCOVID, Google Scholar, Science Direct, and clinicaltrials.gov were the databases utilized.

## Results

Evidence from ongoing clinical trials has shown promise with antiviral medications such as remdesivir, as well as corticosteroids, and convalescent plasma for severe cases of COVID-19. There is still, however, some conflicting evidence on the true benefits of these treatments. Other medications such as interferons, monoclonal antibodies, immune modulators, do not have enough clinical evidence of their safety and efficacy in COVID-19 patients for their recommended use. The role of anticoagulants and pulmonary vasodilators is still being explored. The efficacy of hydroxychloroquine is yet to be demonstrated in COVID-19 patients and is currently no longer recommended. Experimental medications targeting specific viral proteases are future promising therapies.

## Conclusions

The retinue of medications being used to treat COVID-19 is evolving and expanding as more clinical trials provide results. Several potential medication therapies are currently being investigated. While awaiting an approved safe and efficacious medication to treat this virus, a periodic review of on-going research is highly encouraged.

## INTRODUCTION

In the past century, the world has gone through pandemics such as the 1918 H1N1 influenza pandemic, the 1957 H2N2, and 1968 H3N2 pandemics which have brought about advances in science and led to the development of new medications and vaccines. The world has been significantly impacted by the coronavirus-19 (COVID-19) outbreak caused by the novel coronavirus-2 (SARS-CoV-2) and the race is on to find a vaccine. In the interim, various medications are being used. SARS-CoV-2 is a single-stranded RNA beta-coronavirus whose genome encodes structural proteins, non-structural proteins, and accessory proteins.[1] It appeared for the first time in Wuhan, China, at the end of 2019 and is presently being transmitted by human to human transmission.[2,3] Affected individuals demonstrate a wide range of clinical manifestations from asymptomatic, mildly symptomatic, to severe viral pneumonia with respiratory failure, multiorgan and systemic dysfunctions in terms of sepsis and septic shock, and death.[4,5]

By the 7th of September 2020, there were over 27 million confirmed cases of COVID-19 and 881,464 deaths worldwide, reported to World Health Organization (WHO) with the highest cases in the United States of America, India,

and Brazil.[6] Various medications have been proposed and applied to control COVID-19 based on prior experiences with other viral infections such as Ebola, Human Immunodeficiency Virus (HIV), 2003 Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), and the 2012 Middle East Respiratory Syndrome coronavirus (MERS-CoV)).[7,8] However, some of these medications have been shown to lack efficacy against this virus or have been associated with serious adverse effects as in the case of chloroquine and hydroxychloroquine.[9,10]

Coronaviruses are a group of large, enveloped, positive-sense single-stranded RNA viruses found in humans, birds, and other mammals. They cause respiratory tract infections in humans and birds which can range from mild to fatal. They also cause gastrointestinal and neurologic disease in other mammals. SARS-CoV-2 is the third coronavirus that has caused severe disease in humans and spread globally in the past 2 decades.[11] Through genetic recombination and variation, coronaviruses can adapt to new hosts and infect them. The pathophysiology of this virus has been studied and extensively discussed.[11–15] A thorough review of the repurposed medications used since the outbreak and experimental medications in clinical trials is presented.

## METHODS

A literature search was conducted to cover the period of January-September 2020. PubMed, LitCOVID, Google Scholar, Science Direct, and clinicaltrials.gov were the databases used. "*Medications*", "*treatment*", "*therapeutics*", "*pharmacological management*", "*COVID-19*", "*SARS-CoV-2*" were the keywords used in the search engines without considering any restriction of language to identify potential published studies. EndNote X 7.0 software was used to exclude duplicates from searched data. Missing studies were identified by checking the reference list of the selected articles. Information on ongoing clinical trials was obtained from clinicaltrials.gov. Extra information was obtained from case series, case reports, review articles, and randomized clinical trials describing the outcomes of medications used for SARS-CoV-2 treatment, as well as the rationale behind their use. Studies with only abstracts and those without results were excluded from this review.

## RESULTS AND DISCUSSION

### ANTI-INFLAMMATORY AGENTS

### CORTICOSTEROIDS

Corticosteroids include dexamethasone, prednisone, methylprednisolone, and hydrocortisone. Corticosteroids exert their anti-inflammatory effect by inhibiting pro-inflammatory transcription factors. They have been used in a wide range of inflammatory conditions. There is concern about inhibiting the immune system and decreased viral clearance with the use of corticosteroids in COVID-19 patients. This is because the use of corticosteroids in other coronavirus outbreaks did not improve mortality but rather was associated with decreased viral clearance and high rate of complications.[16,17] A study that was done early in the pandemic showed no difference in mortality with the use of corticosteroids in COVID-19 patients.[18] Dexamethasone has been studied for use in the treatment of or prevention of organ dysfunction and lung injury from SARS-CoV-2-induced inflammation. The RECOVERY trial (NCT04381936) arm of dexamethasone showed that the use of this medication in patients hospitalized with COVID-19 resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support.[19] It is not yet known if this may make a positive impact on COVID-19 treatment. However, it is important to note that corticosteroids are the first and so far, only medications to significantly improve survival in hospitalized COVID-19 patients. Moreover, these medications have been around for a while, are cheap, widely available, and have been extensively studied and used. In the REMCAP clinical trial (NCT02735707) of patients with severe COVID-19, hydrocortisone treatment resulted in a 93% probability of superiority with regard to improve odds in organ support free days within 21 days compared to 80% probability in the no hydrocortisone group.[20] Although this trial was stopped early due to results of the RECOVERY trial which showed positive results with the use of corticosteroids, it suggests a beneficial use of steroids in severely ill COVID-19 patients. A recent study of methylprednisolone showed an improvement in oxygenation and no deaths in 15 critically ill COVID-19 patients with no negative impact on virus removal.[21] It is unclear whether or not dexamethasone and other corticosteroids have deleterious effects on viral clearance when used for less severe COVID-19 cases. Further clinical trials would be useful in clarifying this. Although there are numerous side effects of corticosteroid use, the most important of which may be prolonged shedding of the virus; the benefits of low dose steroids in critically ill patients who require oxygen may likely outweigh the risks.

### NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drugs because they have a wide range of use like anti-inflammation, anti-pyrexia. At the beginning of the COVID-19 outbreak, the French Minister of Health made a recommendation to alert healthcare workers to avoid the use of anti-inflammatory medications like ibuprofen or cortisone, claiming it could aggravate infections and make it worse.[22] This was because a study done suggested that the SARS-CoV-2 virus has an increased affinity for the Angiotensin-Converting Enzyme-2 (ACE2) receptor and Ibuprofen, an NSAID has been known to increase the production of ACE2 and increase the expression of the ACE receptors.[23,24] This was later refuted by the World health organization, who stated that there was no evidence that NSAIDs like ibuprofen could worsen the outcome of the disease. A cohort study done on COVID-19 patients showed that there was no difference in outcome between Ibuprofen users and acetaminophen users.[25] Indomethacin is another NSAID that has exhibited potent antiviral activity against canine coronavirus, by dramatically inhibiting virus replication and protecting the host cell from virus-induced damage. This activity was also observed

*in vivo* and against human SARS-CoV.[26] Indomethacin does not affect coronavirus binding or entry into host cells, but acts by blocking viral RNA synthesis at cytoprotective doses.[26] This may be of possible benefit in patients affected by SARS-CoV-2. The effects of another NSAID naproxen in patients with COVID-19 is also yet to be established. Noting that a major side effect of NSAIDs is bleeding from gastrointestinal ulcers and that severe COVID-19 patients end up with disseminated intravascular coagulopathy (DIC) and bleeding, more research is needed to ascertain the dose at which these medications are safe to use in COVID-19 patients and if they are of any benefit.

## COLCHICINE

Colchicine is a medication used in gout and familial Mediterranean fever. It functions by disrupting cytoskeletal functions through inhibition of beta-tubulin polymerization into microtubules, which prevents activation, degranulation, and migration of neutrophils thereby showing anti-inflammatory properties. Colchicine also acts as an anti-oxidative and anti-fibrotic agent. In an animal model of bronchopulmonary dysplasia, treatment with colchicine showed a reduction in inflammatory markers [Interleukin-6(IL-6) and Tumor Necrosis Factor-alpha (TNF-$\alpha$)].[27] Colchicine may therefore help mitigate the cytokine storm associated with COVID-19 infection as high levels of IL-6 have been seen in these patients. A case report of a patient with moderate COVID-19 treated with colchicine showed an improvement in symptoms and a reduction in levels of IL-6.[28] A cohort study of 9 patients with moderate COVID-19 treated with colchicine showed an improvement in symptoms within 72 hours.[29] This study also postulated that treatment with colchicine early in the disease process may be more beneficial before the onset of ARDS. However, the true efficacy of this medication in COVID-19 patients is still unknown. There are several ongoing clinical trials to confirm the benefit and utility of this medication in COVID-19 patients.

## ANTIVIRALS

There is presently no approved antiviral therapy for COVID 19, however, clinical trials are presently ongoing to assess for the efficacy of antivirals as monotherapy or as a combination with other drug classes. A study done early on in the pandemic suggested that antiviral drugs if administered shortly after symptom onset can reduce infectiousness to others by reducing viral shedding in the respiratory secretions of patients as it has been shown that SARS-CoV-2 viral load in sputum peaks at around 5–6 days after symptom onset and lasts up to 14 days.[30] Antivirals that have been used in COVID-19 patients include remdesivir, favipiravir, umifenovir, lopinavir/ritonavir, sofosbuvir, daclatasvir, and ribavirin.

## FAVIPIRAVIR AND UMIFENOVIR

Favipiravir and umifenovir (Arbidol) were originally used in Influenza patients. Favipiravir works by inhibiting RNA-dependent RNA polymerase thereby inhibiting viral replication in the host cell. Umifenovir works by direct viricidal activity and interaction with viral proteins and lipids. A randomized controlled clinical trial comparing the use of favipiravir to umifenovir showed a shorter recovery time of mild to moderate COVID-19 patients with cough and fever in the favipiravir group compared to the umifenovir group.[31] There was no difference in outcome for patients with severe COVID-19 who were on oxygen therapy or required ventilation. A study done comparing treatment with umifenovir to lopinavir/ritonavir in COVID-19 patients showed no viral load in the umifenovir group compared to 44% in the treatment group thereby concluding that umifenovir monotherapy may be superior to lopinavir/ritonavir.[32] However, another study done showed that umifenovir use in COVID-19 patients did not accelerate SARS-CoV-2 clearance and was associated with a longer hospital stay.[33] These medications are presently under multiple clinical trials, but available data have not shown significant efficacy as a therapy for COVID 19.

## REMDESIVIR

Remdesivir is an antiviral medication that works by binding to viral RNA-dependent RNA polymerase thereby inhibiting viral replication. Remdesivir was previously manufactured for use in Ebola patients however it lacked efficacy against the virus. A National Institute of Health (NIH)-sponsored, multinational, randomized, double-blind placebo-controlled trial in hospitalized adults with COVID-19 showed that remdesivir reduced time to recovery especially in patients who required supplemental oxygen.[34] However, this study did not show any benefit in patients with mild to moderate COVID-19. In another study, a cohort of patients hospitalized for severe COVID-19 who were treated with remdesivir for compassionate use, clinical improvement was observed in 68% of these patients.[35] A multinational randomized clinical trial of remdesivir in patients with moderate COVID-19 showed an improvement in clinical status on day 11 in those who were on a 5-day course of remdesivir compared to standard care.[36] However, there was no difference in the 10-day course compared to the standard of care. There are also no clinical trials in patients with mild COVID-19 to determine if this medication would be more efficacious early in the disease process. Limitations to its use include cost and availability. The true efficacy and benefit of this medication are unknown and more clinical trials in all age groups and stages of the disease are needed.

## LOPINAVIR/RITONAVIR

Lopinavir and ritonavir are protease inhibitors used in treating HIV infection. Lopinavir has shown an antiviral effect against the SARS-CoV-2 virus in Vitro.[37] A study of 44 patients with mild/moderate COVID-19 in which 21 patients were assigned to receive lopinavir/ritonavir compared to 16 receiving umifenovir and 7 controls showed that were was no difference in the improvement of symptoms among all 3 groups.[38] Another study of a total of 199 patients with laboratory-confirmed SARS-CoV-2 infection, treatment with lopinavir/ritonavir was not associated with a difference from standard care in the time to clinical im-

provement.[39] A meta-analysis of COVID-19 patients treated with lopinavir/ritonavir showed a slight reduction in the risk of requiring invasive mechanical ventilation, developing respiratory failure, or acute respiratory distress syndrome. However, it did not lead to any difference in the duration of hospitalization.[40] The available evidence does not show the true benefit of this medication. However, evidence from ongoing clinical trials should be available soon to inform physicians on the efficacy of this medication combination in COVID-19 patients.

RIBAVIRIN

Ribavirin is an antiviral medication used to treat hepatitis C, respiratory syncytial virus, and some viral hemorrhagic fevers such as Lassa fever. It is a nucleoside inhibitor and interferes with RNA metabolism required for viral replication. Studies have shown that ribavirin did not inhibit previous coronaviruses and did not improve survival in other outbreaks.[41–43] However, due to the lack of any medications for this present coronavirus outbreak, ribavirin was still applied. A retrospective cohort study done on critically ill COVID-19 patients showed that ribavirin therapy was not associated with improved negative conversion time for the SARS-CoV-2 test or an improved mortality rate compared to controls.[44] In a prospective, open-label, randomized, phase 2 trial in adults with COVID-19 ribavirin was used in combination with Interferon $\beta$-1b and lopinavir/ritonavir as triple therapy.[45] The triple therapy group had a significantly shorter median time from the start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days); hazard ratio 4·37 [95% CI 1·86–10·24], *P*=0·0010). It is unclear if this was due to ribavirin or the other medications that were also used. With the currently available research, there is no evidence for the use of ribavirin in COVID-19 patients.

SOFOSBUVIR AND DACLATASVIR

Sofosbuvir and daclatasvir are direct-acting antivirals (DAAs) that work by binding to hepatitis C virus (HCV) NS5B and NS5A RNA dependent polymerases respectively thereby inhibiting viral replication. They are used in combination with ribavirin and interferon to treat hepatitis C infection. They have been applied for use in COVID-19 patients as in-vitro studies have demonstrated some antiviral effects against SARS-CoV-2.[46] Studies done have shown promise in the treatment of COVID-19 patients by shortening clinical recovery and duration of hospitalization.[47–49] Limitations to these studies are the small sample sizes, as well as all studies being from one region. Therefore, more research is needed to evaluate their true benefits. Several clinical trials are ongoing to determine if they are of benefit in SARS-CoV-2 infection.

IMMUNOMODULATORS

INTERLEUKIN-*1* INHIBITORS *(*ANAKINRA*,* CANAKINUMAB*,* RILONACEPT*)*

Interleukin-1(IL-1) family is a group of 11 cytokines, which induces a complex network of proinflammatory cytokines and via expression of integrins on leukocytes and endothelial cells, regulates and initiates inflammatory responses.[50] IL-1 $\alpha$ and IL-1 $\beta$ are the strongest pro-inflammatory cytokines. Interleukin 1 (IL-1) is a potential target of therapy in COVID-19 patients during the cytokine storm phase when pulmonary macrophages are hyperactivated, releasing IL-1 and other cytokines. IL-1 inhibitors include anakinra, canakinumab, rilonacept. There are currently no randomized clinical trials that assess the utility or safety of IL-1 inhibitors in severe COVID-19 patients. Preliminary evidence from a retrospective study on COVID-19 patients treated with high dose anakinra showed an improvement in respiratory function in 72% of patients compared to 56% in the standard treatment group and a 90% survival rate compared to 56% in the standard treatment group.[51] Another cohort study done showed that anakinra reduced both the need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19.[52] Randomized clinical trials are needed to assess the efficacy, dosing, and adverse effects of these medications in patients with severe COVID-19. There are ongoing clinical trials to determine the benefits of these medications in patients with COVID-19.

INTERLEUKIN-*6* INHIBITORS *(*TOCILIZUMAB*,* SARILUMAB*,* SILTUXIMAB*)*

Patients with severe COVID-19 exhibit high serum levels of IL-6 as well as other pro-inflammatory cytokines.[53] Elevated levels of IL-6 were associated with a worse prognosis.[54] It, therefore, follows that inhibiting these cytokines may lead to improved outcomes in these patients. Tocilizumab is the only IL-6 inhibitor that has been used in severe COVID-19 patients and has shown an improvement in outcome. It is originally approved by the FDA for rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome. Studies done on COVID-19 patients with tocilizumab showed a reduction of fever and IL-6 levels, reduced need for oxygen therapy and mechanical ventilation, and improved radiologic lung findings.[55–57] A large retrospective multicenter cohort study also showed a reduced risk of mechanical ventilation and death with the use of tocilizumab irrespective of the route of administration.[58] Clinical trials are ongoing to study the effect of tocilizumab on COVID-19 patients. Preliminary results from the COVIDOSE trial showed that low-dose tocilizumab was associated with rapid improvement in clinical and laboratory measures of hyper inflammation in hospitalized patients with COVID-19.[59] Ongoing clinical trials to determine the safety and efficacy of tocilizumab, as well as other IL-6 inhibitors, would shed more light on the use of this class of drugs in COVID-19 patients.

JANUS KINASE *(*JAKS*)* INHIBITORS *(*BARICITINIB*,* RUXOLITINIB*)*

Janus Kinases (JAKs) are transmembrane proteins that are required for and increase the intensity of signal growth factors and cytokines to host cells. Janus Kinase inhibitors (JAKi) may exert dual anti-inflammatory (blockade of multiple,

pro-inflammatory cytokines simultaneously) and anti-viral effects (impeding cellular viral endocytosis) thereby being superior to other immunomodulators.[60] There are several ongoing, randomized controlled trials evaluating the therapeutic potential of Janus Kinase inhibitors (JAKi) in severe COVID-19. JAKi is FDA approved for use in the treatment of adults with rheumatoid arthritis, myelofibrosis, polycythemia vera, and steroid-refractory acute graft versus host disease. They are proposed for use in severe COVID-19 because they inhibit the JAK-STAT signaling pathway involved in immune regulation. An open-label trial in Italy showed a significant reduction in fever, breathlessness, cough as well as improvement in pulmonary function test and lower C-reactive protein levels in patients treated with baricitinib compared to controls.[61] A meta-analysis of patients treated with JAKi showed that recipients had significantly reduced odds of mortality (OR, 0.12; 95%CI, 0.03-0.39, *P*=0.0005) and ICU admission (OR, 0.05; 95%CI, 0.01-0.26, *P*=0.0005), and had significantly increased odds of hospital discharge (OR, 22.76; 95%CI, 10.68-48.54, *P*<0.00001), when compared to standard treatment group.[62] Limitations to the use of JAKi include the risk of venous thromboembolism which is already a complication of severe COVID-19. This is a potential side effect of baricitinib but not ruxolitinib. As a class, however, it is important to keep this adverse effect in mind when attempting to use JAKi for severe COVID-19 patients due to their already prothrombotic state brought on by the SARS-CoV-2. Several clinical trials are still ongoing to weigh the risk-benefit of this treatment in COVID-19 patients.

## TUMOR NECROSIS FACTOR (TNF) INHIBITORS (ADALIMUMAB, INFLIXIMAB, ETANERCEPT)

TNF is a cytokine involved in systemic inflammation. It induces fever, apoptosis, cachexia, inflammation, and inhibits tumorigenesis and viral replication. Its primary function is immune regulation and it responds to sepsis via IL-1 and IL-6 producing cells. It has been reported that the binding of SARS-CoV-2 to angiotensin-converting enzyme (ACE)-2 induces TNF$\alpha$-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, which facilitates viral entry and causes tissue damage through TNF$\alpha$ production.[63] TNF inhibitors are FDA approved for several autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis. The anti-inflammatory properties of TNF inhibitors suggest that they may be helpful with the inflammation associated with COVID-19. Side effects of superimposed bacterial and fungal infection should be kept in mind when using these medications in COVID-19 patients given their risk of overwhelming sepsis. There are no studies that have demonstrated their benefits in COVID-19 patients however two clinical trials investigating infliximab are underway. More clinical trials are needed for this class of medications considering their already established safety profile.

## GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR (GM-CSF) INHIBITORS

Most of the lung damage seen in severe COVID-19 patients is driven by a surge in inflammatory cytokines [interleukin-6, interferon-$\gamma$, and granulocyte-monocyte colony-stimulating factor (GM-CSF)]. GM-CSF is a pro-inflammatory cytokine. It also stimulates epithelial repair and barrier restoration through direct interaction with the alveolar epithelial cells, thereby providing a lung-protective effect.[64] GM-CSF can have a dual role as a pro-inflammatory and regulatory cytokine, depending on the dose and presence of other relevant cytokines.[65] Levels of GM-CSF have been shown to be higher in patients with COVID-19 compared to healthy controls.[18] This means that there are 2 targets for GM-CSF in COVID-19 patients. GM-CSF can be used as a barrier to protect the lung tissues or it can be inhibited to prevent its pro-inflammatory effect with other cytokines. Sargramostim and molgramostim were investigated in clinical trials of patients with acute lung injury and severe sepsis with respiratory dysfunction respectively.[66,67] There was no improvement in survival in both groups however, there was an improvement in gas exchange and functional activation of pulmonary macrophages in the molgramostim group compared to placebo. To this end, recombinant human GM-CSF is being investigated in clinical trials for use in COVID-19 patients. On the other hand, as GM-CSF is increased in patients with severe COVID-19; inhibition may improve the lung injury associated with cytokine release. A single-center prospective cohort study examined the use of mavrilimumab, a monoclonal antibody GM-CSF inhibitor in non-mechanically ventilated COVID-19 patients with pneumonia and hyper inflammation.[68] The result of this study showed no deaths, improvement in fever, and shorter time to recovery in the mavrilimumab group compared to the control group. The safety and efficacy of this medication have been tested in a phase 2 clinical trial in Rheumatoid arthritis patients.[69] Further studies to determine the role of GM-CSF in COVID-19 patients should be carried out. There are ongoing clinical trials to determine the benefits of inhaled sargramostim in COVID-19 patients. More clinical trials are needed to also determine the effects of GM-CSF inhibitors in COVID-19 patients.

## INTERFERONS

Interferons (IFNs) are a group of signaling glycoproteins produced and released from cells in response to a viral infection. The role of interferons is to inhibit viral replication and activate immune cells. Interferons have been used to treat multiple sclerosis, multiple cancers, and genital warts. Various forms exist which include interferon-$\alpha$ 2b, n3, interferon $\beta$ 1a, 1b, interferon-$\gamma$ 1b. Interferon-alpha was used during the 2003 SARS-CoV outbreak in Canada with good results.[70] The role of interferons in the treatment of COVID-19 patients is still under investigation. A study of interferon 1b given to COVID-19 patients with mild to moderate disease showed a significant reduction in viral shedding, duration of hospital stays as well as improvement in symptoms compared to those treated with lopinavir/ritonavir and ribavirin.[71] This effect was more pronounced among those treated within 7 days of symptom onset. Another study in Wuhan, China of 77 patients treated with interferon-$\alpha$ 2b with or without umifenovir showed a significantly reduced duration of detectable virus in the upper res-

piratory tract and a parallel reduced duration of elevated blood levels for the inflammatory markers IL-6 and C-reactive proteins (CRPs).[72] This study was also done on patients with mild to moderate disease. It is unclear whether interferons would have the same effect on severe COVID-19 patients. Some of the concerning adverse effects of interferon use include fever, flu-like syndrome, and leukopenia which may worsen COVID-19 symptoms. However, these effects were not seen in the patients in the studies mentioned above and may be due to the small sample size. Further clinical trials exploring the effects of this therapy are needed.

### MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are multipotent adult stromal cells present in multiple tissues, including the umbilical cord, bone marrow, and fat tissue. MSCs can regenerate by dividing and can differentiate into multiple tissues including bone, cartilage, muscle, and adipose cells, and connective tissue. MSCs could exert widespread immunomodulatory effects by suppressing the activity of a broad range of immune cells, including T cells, natural killer T (NKT) cells, dendritic cells (DCs), B cells, neutrophils, monocytes, macrophages etc.[73] Mesenchymal stem cell transplant has markedly improved symptoms in COVID-19 patients. A study of 7 patients with COVID-19 including 2 severe cases, infused with MSCs showed an improvement in pulmonary function, reduced inflammatory markers, and increased interleukin-10 (an anti-inflammatory cytokine) within 2 days compared to those patients on placebo.[74] Another case report of an elderly patient with severe COVID-19 in the ICU treated with MSCs for 3 days showed improvement in symptoms and a subsequent negative throat swab test 4 days later.[75] MSC transfusion was not associated with any side effects in these patients indicating that it may be a safe treatment. Of note, the gene expression profile of the recovered MSC was ACE negative and TMPRSS2 negative which indicated that it remained negative for COVID-19.[74] It also continued to show high levels of anti-inflammatory activity indicating that immunomodulatory properties are long term.[76] These preliminary reports indicate that MSC transfusion may be beneficial to patients with severe COVID-19 especially the elderly. Limitations to the use of MSC therapy include high cost, specialized staff, and equipment, transfusion reactions including graft versus host disease, and delayed hypersensitivity reactions. The high cost, specialized staff, and equipment also mean that this therapy may not be readily available in resource-poor countries. There are several ongoing clinical trials to determine the benefit of MSC therapy in COVID-19 patients and results should be available soon.

### STATINS

Statins are lipid-lowering drugs that decrease the cellular cholesterol content by inhibiting hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme in the L-mevalonate pathway of cholesterol biosynthesis thereby lowering hepatic cholesterol concentrations. L-mevalonate pathway downstream products play critical roles in different steps of immune response including immune cell activation, migration, cytokine production, immune metabolism, and survival.[77] Statins have shown immunomodulatory properties and have been used in the treatment of various infectious diseases such as community-acquired pneumonia and influenza. They have also shown benefit in the management of inflammatory and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.[78] To date, there are no randomized controlled clinical trials that have demonstrated the benefit of statins in patients with COVID-19, however, an observational, multinational study that included more than 8,500 hospitalized patients with COVID-19 showed that the use of statins was associated with a better survival rate in these patients.[79] Statins are well studied and generally well-tolerated medications and the rationale for their use in COVID-19 patients is due to its immunomodulatory and anti-inflammatory effects. Limitations to its use may be due to its hepatotoxic side effects which may be compounded by the effect of the SARS-CoV-2 virus on liver cells.[80] However, a randomized controlled clinical trial is needed to further characterize its true benefit.

### ANTIBODY THERAPY

### CONVALESCENT PLASMA

Convalescent Plasma is plasma obtained from patients who have recovered from COVID-19 infection with a high neutralizing antibody titer. COVID-19 convalescent plasma may be used for either prophylaxis of infection or treatment of disease. In a prophylactic mode, the benefit of convalescent plasma administration is that it can prevent infection and subsequent disease in those who are at high risk for disease, such as vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to confirmed cases of COVID-19.[81] Passive antibody administration to prevent disease is already used in clinical practice. For example, patients exposed to hepatitis B and rabies viruses are treated with hepatitis B immune globulin (HBIG) and human rabies immune globulin (HRIG), respectively.[81] There is evidence that convalescent plasma if administered early may be effective in the prevention and treatment of COVID-19 infection.[82,83] A cohort study done in Mayo Clinics with >35000 participants showed that the seven-day mortality rate was reduced in patients transfused within three days of COVID-19 diagnosis compared with patients transfused four or more days after COVID-19 diagnosis.[84] On the other hand, a Chinese open lab, multicenter randomized controlled study evaluating the efficacy and safety of convalescent plasma therapy on 103 COVID-19 patients with severe or life-threatening disease found no significant difference in time to clinical improvement within 28 days, mortality, or time to hospital discharge but clinical improvement was only observed in a subgroup of patients.[85] However, in this study, it was observed that the majority of the 103 patients received their plasma 14 days after symptom onset compared to the Mayo clinic study in which participants received plasma therapy within 3 days of diagnosis. This suggests that convalescent plasma therapy may need to be initiated earlier to be able to see a significant improvement in patients with COVID-19. Although

convalescent plasma has been granted emergency use authorization by the United States Food and Drug Administration (FDA), more clinical trials are still needed to understand the efficacy of this treatment as well as its side effects.

## INTRAVENOUS IMMUNOGLOBULIN *(*IVIG*)*

Intravenous immunoglobulin is a treatment therapy for patients with antibody deficiencies. It is a blood product prepared from the serum of healthy donors. It has been used in the treatment of dermatomyositis, polymyositis, idiopathic thrombocytopenic purpura as well as Kawasaki disease in children. A case series of 5 COVID-19 patients treated with high dose IVIG showed improvement in oxygen saturation and radiographic evidence demonstrated less consolidation.[86] IVIG may be also be used to confer passive immunity. IVIG is associated with the risk of transfer of infectious agents through blood products, as well as hypersensitivity reactions. Since IVIG has been used with a negligible risk of these adverse events, it is safe to say that it may be applied for use in COVID-19 patients. Another potential risk factor for immunoglobulin replacement therapy use in patients with COVID-19 may be due to mitigating antibody response that could interfere with establishing efficient immune responses against viremia.[87] A clinical trial is needed to confirm the benefits of this treatment both as a prophylactic and therapeutic option.

## MONOCLONAL ANTIBODIES

Monoclonal antibodies (MAB) are medications designed in the laboratory that contain specific proteins naturally made by the immune system in response to a pathogen. They can bind directly to portions of the virus that mediate cell entry and attachment thereby preventing disease in early infection. They may also be able to provide short term immunity against SARS-CoV-2. Monoclonal antibodies have been used for years to treat autoimmune diseases and are generally safe. There are no studies that evaluate their effects on COVID-19 patients. However, there are 2 monoclonal antibody medications undergoing clinical trials. REGN-CoV-2 and LY-CoV-555 are being investigated to evaluate their effects in preventing COVID-19 in patients at risk. One major limitation to the use of monoclonal antibodies is the cost involved in manufacturing them. Even if an efficacious MAB is discovered, it would likely be too expensive for routine use.

## ANTICOAGULANTS

Anticoagulants include the heparins; unfractionated heparin and low molecular weight heparin, warfarin, thrombin inhibitors such as argatroban, dabigatran, factor Xa inhibitors e.g. rivaroxaban, fondaparinux. Studies done show that SARS - CoV - 2 causes a “cytokine storm” which is part of the systemic inflammatory response[88] that activates the coagulation cascade, leading to thrombosis. Also, generalized deposition of intravascular thrombi compromises the blood supply of several organs, leading to organ failure[89] similar to findings seen in severe sepsis caused by bacterial infections. SARS-CoV-2 has been shown to cause widespread coagulation which contributes to worse patient outcomes and mortality.[90] Anticoagulant treatment has been shown to improve this outcome.[91] Low Molecular Weight Heparin (LMWH) has been the mainstay of treating deep vein thrombosis (DVT) complications in COVID-19 patients,[92] the dose however needs to be titrated for the benefits to outweigh the risks. One of the serious adverse effects of LMWH is thrombocytopenia which can lead to life-threatening bleeding complications in patients such as these who are already at risk of DIC and multi-organ failure. A meta-analysis of COVID-19 patients admitted in the intensive care unit who were given heparin (unfractionated and low molecular weight heparin) for thromboprophylaxis showed a high failure rate.[93] Argatroban, a direct thrombin inhibitor has been shown to improve thrombotic complications in COVID-19 patients who fail heparin therapy.[94]

The role of other anticoagulants such as warfarin, dabigatran, bivalirudin, need to be investigated. Clinical trials are underway to study the effect of rivaroxaban and fondaparinux in COVID-19 patients with thrombotic complications. Further studies to determine anticoagulant selection and dosage are needed in critically ill COVID-19 patients admitted to intensive care units.

## PULMONARY VASODILATORS

### NITRIC OXIDE

Nitric oxide is an inhaled gas that works by relaxing vascular smooth muscle, resulting in pulmonary vasodilation. Nitric oxide has been used to treat respiratory failure in preterm babies. One of the causes of mortality in severe COVID-19 is respiratory failure due to refractory hypoxemia.[95] Inhaled nitric oxide may be considered for use in COVID-19 patients with ARDS due to its potent vasodilator effect. A study done on 39 patients with moderate COVID-19 showed that 21(53.9%) did not require intubation after treatment with inhaled nitric oxide.[96] However, these patients were also treated with hydroxychloroquine, azithromycin, and IL-6 antagonists so it is unclear if they improved based on the nitric oxide alone or a synergistic effect of one of these medications. A case series of 10 severe COVID-19 patients treated with inhaled nitric oxide did not show any improvement in arterial oxygenation after 30minutes of use.[97] Because of the potential side effects of prolonged inhaled nitric oxide,[98] caution has to be employed in use in severe COVID-19 patients in order not to worsen outcome. The use of nitric oxide (NO) to treat COVID - 19 - related interstitial lung disease has been approved by the US FDA. Further investigation and clinical trials are needed to determine the population of patients who would benefit the most and the optimal dose with the least side effects.

### SILDENAFIL

Sildenafil is a phosphodiesterase (PDE) inhibitor whose mechanism of action is to inhibit PDE-5 thereby increasing cyclic guanosine monophosphate to allow smooth muscle relaxation. It has been used to treat pulmonary arterial hypertension and erectile dysfunction. PDE-5 is highly expressed in the lungs, where its inhibition improves pul-

monary fibrosis, a complication of severe COVID-19 disease.[99] There are no studies that have demonstrated their effects in COVID-19 patients. However, there are ongoing clinical trials to assess their effects. Results should be available soon to know if this cheap and widely available medication is of benefit in COVID-19 patients.

## CONTROVERSIAL THERAPIES

### HYDROXYCHLOROQUINE/CHLOROQUINE PLUS AZITHROMYCIN

Hydroxychloroquine and chloroquine are medications that have been used to treat malaria and rheumatologic conditions. The anti-inflammatory effects of these medications include inhibition of T and B cell receptors thereby decreasing cytokine production by macrophages such as IL-1 and IL-6.[100] These medications have also been shown to inhibit TNF-$\alpha$, interferon-$\alpha$, and $\gamma$.[101,102] These are all inflammatory cytokines that have been implicated in the SARS-CoV-2 cytokine storm. These medications have also demonstrated anti-viral properties against SARS-CoV-2 invitro.[103] Because of the antiviral and anti-inflammatory properties of these medications, researchers proposed that they may be helpful in the treatment of COVID-19 patients. Studies done early in the pandemic showed promise with these medications in the treatment of COVID-19 patients.[104,105] One of these studies was limited to one region and the other was underpowered. As this medication was used in more patients with COVID-19 around the world, conflicting evidence on its efficacy for COVID-19 treatment began to emerge. An observational study of 1376 patients showed that in patients administered hydroxychloroquine, it did not affect time to intubation or death.[106] An NIH sponsored trial of hydroxychloroquine was discontinued as the drug was shown to not be beneficial in hospitalized COVID-19 patients compared with placebo.[107] Another study done on hydroxychloroquine showed that it did not prevent illness compatible with COVID-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure.[108] Azithromycin is a macrolide antibiotic that has also shown some antiviral and anti-inflammatory properties[109,110] thus was recommended for use in COVID-19 patients in addition to hydroxychloroquine/chloroquine. However, a retrospective study done in the US showed that hydroxychloroquine use with or without co-administration of azithromycin did not improve mortality or reduce the need for mechanical ventilation.[111] An important side effect to note of this medication combination is prolonged QT interval which can lead to life-threatening arrhythmias especially in severe COVID-19 patients with underlying cardiovascular disease. A study done on severe COVID-19 patients who were administered high dose chloroquine showed that 18.9% of patients presented with prolonged QT interval compared to 11.1% in the low dose chloroquine group.[112] A meta-analysis of COVID-19 patients treated with hydroxychloroquine/chloroquine with or without azithromycin showed an increased risk of in-hospital mortality and ventricular arrhythmias with the use of any of these medications.[113] This study was later retracted as the authors could not provide their data for subsequent re-analysis.[114] There are several ongoing clinical trials to determine the effects of hydroxychloroquine/chloroquine, hydroxychloroquine/chloroquine plus azithromycin, azithromycin alone as well as hydroxychloroquine with other antiviral medications on COVID-19 patients. Inhaled hydroxychloroquine is also being tested. Some of the clinical trials involving these medications have been suspended or terminated due to concerns about the safety of these medications as well as lack of patient enrollment.

### ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/ ANGIOTENSIN RECEPTOR BLOCKERS (ACEI/ARBS)

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are commonly used antihypertensives that act by inhibiting the renin-angiotensin-aldosterone system (RAAS). These medications are cardio and renoprotective.[115] With the discovery that ACE2, a homolog of ACE, which is richly expressed in heart and lung tissue, aids the fusion of host cells and SARS-CoV-2[116], interest has been generated in what role these medications may play in this disease process. The ACE2 receptor appears to counter regulate RAAS activation by degrading angiotensin II.[117] Concerns about the potentially harmful effect of ACEi in patients with COVID-19 have been expressed because angiotensin-converting enzyme 2 (ACE2) is the receptor-binding site for SARS-CoV-2 in the target cell.[12] In vitro and in vivo studies have demonstrated that ACE inhibitors (ACEIs), as well as angiotensin-II receptor blockers (ARBs), can significantly increase ACE2 expression, thereby facilitating SARS-CoV-2 entry into cells.[118,119] However, evidence from studies done so far show that prior use of ACEi or ARBs do not increase the risk of contracting SARS-CoV-2 or of being hospitalized with severe infection.[120,121] A recent meta-analysis of >28000 patients who were already on these medications had a lower risk of death from COVID-19 compared to patients who were not on these medications.[122] This study also added to the growing body of evidence that the use of ACEi/ARB does not have any association with the severity of disease or even death among patients admitted with COVID-19. The effect of commencing treatment with ACEi/ARBs in patients diagnosed with COVID-19 who were previously not on these medications has not been studied. In the interim, ACEi/ARBs should not be discontinued in patients with COVID-19 already on these medications as this may lead to worsened outcomes considering the high mortality among patients with underlying health conditions a significant number of whom are on these medications. More studies investigating the effects of these medications on the SARS-CoV-2 virus are needed.

## POTENTIAL THERAPIES

### FURIN AND TMPRSS2 INHIBITORS

Furin is a host protease that processes viral fusion proteins and certain bacterial toxins for entry into the human cell. Pre-activation of furin present in human ACE2-expressing cell lines, including lung epithelial and lung fibroblast cell lines enhances SARS-CoV-2 entry into these cells. Cell surface transmembrane protease serine 2 (TMPRSS2) and lyso-

**Table 1. Experimental Medications in Clinical Trials for COVID-19 as of August 2020**

| Drug | Primary Use | Mechanism of Action | Number of Clinical Trials |
|---|---|---|---|
| Apilimod | Ebola virus | Inhibition of viral replication | 1 |
| Aviptadil | Erectile dysfunction | Treatment of Respiratory distress | 3 |
| Opaganib | Cancer, Inflammatory and GI conditions | Inhibition of viral replication | 4 |
| REGN-COV2 | COVID-19 | Virus neutralizing antibody | 4 |
| LY-CoV555 | COVID-19 | Inhibits virus fusion with host cells | 3 |
| PUL-042 | Respiratory viral infections | Stimulates toll-like receptors on lung epithelial cells to initiate an immune system response against pathogens | 2 |
| EDP1815 | Psoriasis | Immune modulator | 2 |

somal cathepsins activate SARS-CoV-2 entry and both have cumulative effects with furin on SARS-CoV-2 entry. This goes to follow that inhibiting furin and TMPRSS2 may prevent SARS-CoV-2 from entering the host cell and causing COVID-19 infection. TMPRSS2 is more abundant in the lungs while furin is expressed in other organs. This may explain why SARS-CoV-2 is capable of invading and damaging multiple organs. This is not as straightforward, however, because several other factors such as human airway trypsin-like protease(s) also play a role in the fusion of SARS-CoV-2 to the target cell.[123] More in vitro and in vivo studies are needed to examine the role of this enzyme and its use as a potential treatment strategy. Camostat mesylate, a TMPRSS2 inhibitor has been used in Japan for the treatment of acute symptoms of chronic pancreatitis and post-operative reflux. Experimental mouse studies showed that camostat was effective in preventing death following a lethal dose of SARS-CoV.[124] A study done using the TMPRSS2 inhibitor camostat on a sample of SARS-CoV-2 from a patient showed that the medication blocked the entry of the virus into the lung cell.[12] Another TMPRSS2 inhibitor nafamostat mesylate used in Asian countries as an anticoagulant therapy for patients undergoing continuous renal replacement therapy due to acute kidney injury, blocked SARS-CoV-2 infection of human lung cells with markedly higher efficiency than camostat mesylate.[125] The fact that it is being used as an anticoagulant may be of further benefit in critically ill COVID-19 patients who are at risk of thrombosis and thrombotic complications. There are ongoing clinical trials to test the benefits of these medications in COVID-19 patients. Medication to inhibit both furin and TMPRSS2 would likely be of the most benefit in preventing viral replication in host cells.

Bromhexine hydrochloride is a mucolytic agent used in over the counter (OTC) cough suppressants. It has also been identified as a selective TMPRSS2 inhibitor.[126] An open-label randomized clinical trial of 78 patients in Iran showed that there was a significant reduction in ICU admissions, intubation, and death in the bromhexine treated group compared to standard therapy.[127] Considering that this medication has minimal side effects and an established safety profile, it could make a positive impact on the management of patients with SARS-CoV-2 both as a prophylactic and therapeutic agent. There are ongoing clinical trials to test this theory.

## MAIN PROTEASE ($M^{PRO}$) INHIBITORS

Specific protease inhibitors have been used successfully for years to treat HIV and HCV. Main protease ($M^{pro}$) is an enzyme in coronaviruses that cuts the polyproteins translated from viral RNA to yield functional viral proteins. Inhibiting the activity of this enzyme would block viral replication. A study done with experimental compounds ebselen and N3 to inhibit this enzyme in SARS-CoV-2 cells has shown promising results in vitro.[128] Another study showed that a prodrug GC370, a dipeptidase protease inhibitor, and its parent drug GC373 used in feline coronavirus infection are potent inhibitors of SARS-CoV-2 replication in cell culture by inhibiting the $M^{pro}$ enzyme.[129] These studies lay the groundwork for further experimental studies and clinical trials of specific protease inhibitors for SARS-CoV-2 infection.

## EXPERIMENTAL MEDICATIONS

Some experimental medications in clinical trials for COVID-19 are presented in table 1 below.

## OTHER MEDICATIONS

Several other medications are being considered for the treatment of COVID-19 patients and currently undergoing clinical trials.

Ivermectin, an antiparasitic medication which has been shown to have inhibitory effects on the replication of the SARS-CoV-2 virus in-vitro.[130]

Nitazoxanide (NTZ), anti-protozoal medication has been shown to have anti-viral activity against different viruses such as coronaviruses, influenza viruses, Ebola virus, hepatitis B and C viruses.[131–135] NTZ has also exhibited in vitro inhibition of SARS-CoV-2 virus.[136] Other beneficial fea-

tures of NTZ include its ability to suppresses the production of pro-inflammatory cytokines[137] emphasizing its potential to manage COVID-19-induced cytokine storm and its reported efficacy of bronchodilation of the extremely contracted airways in COVID-19 patients.[138]

Pentoxifylline is a hemorheological agent used in the treatment of intermittent claudication. The properties of pentoxifylline which may be helpful in COVID-19 patients include reducing the production of the inflammatory cytokines without deleterious effects on the immune system which may delay viral clearance, restoring the balance of the immune response, reduce damage to the endothelium and alveolar epithelial cells, improve circulation, prevent microvascular thrombosis and improve ventilatory parameters.[139]

Anti-fibrotic agents (pirfenidone, nintedanib) have also been proposed for use in treating the complication of pulmonary fibrosis following ARDS in COVID-19 patients. These agents are already approved for use in the treatment of idiopathic pulmonary fibrosis. Pirfenidone especially has been proposed due to its anti-inflammatory, anti-oxidative, and anti-fibrotic properties.[140] It has also been shown to downregulate ACE receptor expression which is the binding receptor for the S protein of the SARS-CoV-2 virus.[141] This is an area of research in treating COVID-19 patients that are lacking and clinical trials are needed to evaluate the effects of this medication based on the mechanism of action.

There is currently no evidence for the use of zinc and vitamin C in the prevention and treatment of COVID-19 patients. However, there are ongoing clinical trials to test the benefits of these medications as a combination with other medications. Vitamin D deficiency has been shown to increase the risk of contracting COVID-19.[142] However, it is unclear if supplementation could reduce this risk. Several clinical trials to ascertain the benefit of vitamin D supplementation in the prevention and treatment of COVID-19 are ongoing.

## REGIONAL VARIATIONS IN COVID-19 TREATMENTS

COVID-19 treatments vary across countries and regions. In the United Kingdom (UK), the RECOVERY trial which involved 176 hospitals in the National Health Service system and about 12000 patients has made a huge and positive impact on COVID-19 treatment in the region.[19,143] This trial revealed that lopinavir, ritonavir, and hydroxychloroquine were not effective medications for severely ill COVID-19 patients and that dexamethasone improved mortality in these patients. This was quickly adopted in other European countries and may have aided in reducing the mortality associated with the virus in some parts of this region. The RECOVERY trial is still ongoing and is currently investigating the efficacy of low dose dexamethasone in children with COVID-19, as well as azithromycin, tocilizumab, and convalescent plasma in adult patients with the virus.

The United States on the other hand which has the most deaths in the world has different treatment protocols which may be because the healthcare system is not as cohesive as in the UK. This lack of cohesiveness may be a reason the mortality rate is very high. Different treatment protocols across different regions in the US may also be part of the problem. The US NIH has approved the use of steroids, remdesivir, and convalescent plasma for treating COVID-19 patients. There are other issues involved with the treatment of COVID-19 in the US such as the political climate but this is beyond the scope of this review.

Ivermectin is being used as a treatment protocol in many South American countries. This was based on a paper which stated that this medication lowered in-hospital mortality in COVID-19 patients.[144] It was later discovered that the methodology used was flawed and the study was retracted. However, many South American countries continue to prescribe this medication for patients with the virus even outside of clinical trials. Other substances such as chlorine dioxide are also being used and have ultimately led to chlorine dioxide poisoning. However, a study (NCT04343742) on clinicaltrials.gov is currently recruiting to test the effectiveness of this agent in COVID-19 patients.

Traditional Chinese medicine has also been used for COVID-19 patients and is said to improve outcomes in these patients.[145,146] This was however not done in a clinical trial, and the dosing, efficacy, and side effects of these treatments are not known. Published literature on the treatment protocol for COVID-19 in India includes hydroxychloroquine, chloroquine, azithromycin, and convalescent plasma.[147] Alternative medicine options such as ayurvedic potions (Ukalo), homeopathic drops (*Arsenicum album*) are also being used in India without any proof of efficacy.[148]

In Africa, there is a paucity of data concerning COVID-19 treatments. However, a herbal remedy developed in Madagascar and consisting of *Artemisia annua* (the plant from which the antimalaria drug artemisinin is gotten from) was touted by some African leaders as a cure for COVID-19.[149] There are no results yet from clinical trials on artemisinin in COVID-19 patients. Hydroxychloroquine and chloroquine were also being used especially as prophylaxis. However, researchers have cautioned that this may lead to widespread malaria resistance which is endemic in the region.[150]

In Australia and New Zealand, hydroxychloroquine/chloroquine and lopinavir/ritonavir were initially being tested in COVID-19 patients in the ASCOT trial (ACTRN12620000445976) however these arms of the trial were discontinued after the results of the RECOVERY trial were published but the convalescent plasma arm remains.[151] Remdesivir and dexamethasone became the new standard of care after positive results with the use of these medications in COVID-19 patients were published.[152] These countries, however, have one of the fewest cases worldwide and the lowest deaths. This may be because public health measures were largely used to contain the virus.

## RECOMMENDATIONS AND CONCLUSIONS

To treat this disease, the virus has been targeted at different stages of its life cycle and attempts have been made to modulate the body's immune response to it. Each medication and treatment modality may be efficacious at different stages of illness and also in different manifestations of disease as discussed above. One limitation to getting a safe and efficacious treatment is the disproportionate number of

cases across regions which has slowed recruitment of a diverse patient population needed for robust clinical trials.

Until a definitive treatment is available, public health interventions such as social distancing, mask-wearing, contact tracing, and increased testing which limit the spread of the virus are paramount. While these efforts are being deployed, medications may bridge the gap pending the development of a vaccine. To date, there are no approved medications for the treatment of COVID-19 outside of clinical trials. Physicians should therefore take into consideration the side effects of these repurposed medications when prescribing them for COVID-19 patients. Since we are in the middle of a pandemic with a new virus, it is important for medications to be used systematically and adequate documentation of treatment outcomes and side effects made. This would help with retrospective analysis of data which may throw more light on treatment modalities and aid in future research. Because a lot of the available data from medications were used together with the standard of treatment at the time (hydroxychloroquine/chloroquine,) which has now been shown to not be beneficial and associated with possible serious adverse effects and/or antiviral medications (some of which have not been shown to be efficacious against this virus); there is the need for more clinical trials without the confounding effects of these medications. Also, the effects of hydroxychloroquine/chloroquine need to be confirmed with more retrospective studies on patients who had already had these medications. Experimental medications and compounds also need to go through the proper stages of randomized clinical trials for their best use and benefit to be ascertained. These experimental medications if found to be effective against this virus may need to be mass-produced for low to middle-income countries to also benefit because only when an efficacious treatment is widely available can we be able to end this pandemic globally. Sanders et al[153] in their study stated some recommendations and guidelines for use of medications during this pandemic such as taking into account the potential for toxicity with these repurposed medications, considering the use of IL-6 inhibitors in certain patients, continuing ACEis/ARBs in patients who need them, and enrolling patients who qualify in clinical trials for certain medications. In addition to these, we recommend continuing statin medications and hydroxychloroquine in patients who need them, taking into account the various comorbidities of each patient to limit polypharmacy as much as possible, as well as the severity of the illness when prescribing these medications.

The world appears to be moving on from COVID-19 while awaiting a vaccine but patients affected by this virus continue to be hospitalized with high mortality. Considering the mounting body of evidence for and against the various medications that have been used in the fight against COVD-19, this review is needed to keep track of where we are concerning therapeutics for COVID-19 and what the future holds. Although developing an effective vaccine is viewed as the ultimate endpoint in preventing the morbidity and mortality associated with this virus, vaccines depend on individual participation. Appropriate medications with an established safety profile should be used in the interim when primary prevention is inadequate. More robust randomized controlled clinical trials of these medications are needed most importantly to include individuals of all age groups, gender, and race for more generalizable findings to ensue.

ACKNOWLEDGMENTS

The authors will like to thank the following individuals for their assistance throughout the study: Dr. Iziegbe Fenemigho, Dr. Abdullahi Sulaiman.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

AUTHORSHIP CONTRIBUTIONS:

O.O- Introduction and literature review, methods, interferons, mesenchymal stem cells, antibody therapy, anticoagulants, pulmonary vasodilators, hydroxychloroquine, other medications, experimental medications, potential therapies, regional treatment of COVID-19, recommendations, conclusion. H.W- Critical revision for intellectual content, editing. S.T- Antivirals, anti-inflammatory medications. A.N- Some immune modulators, convalescent plasma. I.E- Controversial Therapies (ACEis/ARBs).

COMPETING INTERESTS

The authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author), and declare no conflicts of interest.

CORRESPONDENCE TO:

Oyiyechukwu Anne Onwudiwe, MBBS
1650, Selwyn Avenue, Suite 6H,
New York, New York, 10457, USA.
ooyiye@yahoo.com

Submitted: September 24, 2020 GMT, Accepted: September 25, 2020 GMT

# REFERENCES


1. Huang D, Lian X, Song F, et al. Clinical features of severe patients infected with 2019 novel coronavirus: A systematic review and meta-analysis. *Ann Transl Med*. 2020;8(9):576-576. doi:10.21037/atm-20-2124

2. Guo Y-R, Cao Q-D, Hong Z-S, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Military Med Res*. 2020;7(1). doi:10.1186/s40779-020-00240-0

3. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/nejmoa2001316

4. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/nejmoa2002032

5. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*. 2020;19(3):149-150. doi:10.1038/d41573-020-00016-0

6. Organization WH. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/. Accessed August 23, 2020.

7. Maurya VK, Kumar S, Bhatt MLB, Saxena SK. Therapeutic Development and Drugs for the Treatment of COVID-19. In: *Medical Virology: From Pathogenesis to Disease Control*. Springer Singapore; 2020:109-126. doi:10.1007/978-981-15-4814-7_10

8. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *BST*. 2020;14(1):69-71. doi:10.5582/bst.2020.01020

9. Administration UFaD. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed August 23, 2020.

10. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2020;383(6):517-525. doi:10.1056/nejmoa2016638

11. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi:10.1056/nejmoa2001017

12. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-280.e8. doi:10.1016/j.cell.2020.02.052

13. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. 2020;11(1):1620.

14. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci USA*. 2020;117(21):11727-11734. doi:10.1073/pnas.2003138117

15. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;324(8):782. doi:10.1001/jama.2020.12839

16. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. doi:10.1371/journal.pmed.0030343

17. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. doi:10.1164/rccm.201706-1172oc

18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506. doi:10.1016/s0140-6736(20)30183-5

19. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *New England Journal of Medicine*. 2020.

20. Investigators TWCftR-C. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *Jama*. 2020.

21. Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. *Journal of Allergy and Clinical Immunology*. 2020;146(2):325-327. doi:10.1016/j.jaci.2020.05.021

22. Day M. Covid-19: Ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ*. March 2020:m1086. doi:10.1136/bmj.m1086

23. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet Respiratory Medicine*. 2020;8(4):e21. doi:10.1016/s2213-2600(20)30116-8

24. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H. Structural basis of receptor recognition by SARS-CoV-2. 2020;581(7807):221-224.

25. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clinical Microbiology and Infection*. 2020;26(9):1259.e5-1259.e7. doi:10.1016/j.cmi.2020.06.003

26. Amici C, Di Caro A, Ciucci A, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. *Antiviral therapy*. 2006;11(8):1021-1030.

27. Ozdemir R, Yurttutan S, Talim B, et al. Colchicine protects against hyperoxic lung injury in neonatal rats. *Neonatology*. 2012;102(4):265-269. doi:10.1159/000341424

28. Gandolfini I, Delsante M. COVID-19 in kidney transplant recipients. 2020;20(7):1941-1943.

29. Della-Torre E, Della-Torre F, Kusanovic M, et al. Treating COVID-19 with colchicine in community healthcare setting. *Clinical Immunology*. 2020;217:108490. doi:10.1016/j.clim.2020.108490

30. Mitjà O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. *The Lancet Global Health*. 2020;8(5):e639-e640. doi:10.1016/s2214-109x(20)30114-5

31. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv*. March 2020. doi:10.1101/2020.03.17.20037432

32. Zhu Z, Lu Z, Xu T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *Journal of Infection*. 2020;81(1):e21-e23. doi:10.1016/j.jinf.2020.03.060

33. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study. *Clinical Microbiology and Infection*. 2020;26(7):917-921. doi:10.1016/j.cmi.2020.04.026

34. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *The New England journal of medicine*. 2020.

35. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*. 2020;382(24):2327-2336. doi:10.1056/nejmoa2007016

36. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *Jama*. 2020.

37. Choy K-T, Wong AY-L, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Research*. 2020;178:104786. doi:10.1016/j.antiviral.2020.104786

38. Li Y, Xie Z, Lin W, et al. Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial. *Med*. May 2020. doi:10.1016/j.medj.2020.04.001

39. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799. doi:10.1056/nejmoa2001282

40. Verdugo-Paiva F, Izcovich A, Ragusa M, Rada G. Lopinavir/ritonavir for COVID-19: A living systematic review. *Medwave*. 2020;20(06):e7967. doi:10.5867/medwave.2020.06.7966

41. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. *Clinical Infectious Diseases*. 2020;70(9):1837-1844. doi:10.1093/cid/ciz544

42. Barnard DL, Day CW, Bailey K, et al. Enhancement of the infectivity of SARS-CoV in BALB/c mice by IMP dehydrogenase inhibitors, including ribavirin. *Antiviral Research*. 2006;71(1):53-63. doi:10.1016/j.antiviral.2006.03.001

43. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *Journal of Clinical Virology*. 2004;31(4):304-309. doi:10.1016/j.jcv.2004.07.006

44. Tong S, Su Y, Yu Y, et al. Ribavirin therapy for severe COVID-19: A retrospective cohort study. *International Journal of Antimicrobial Agents*. 2020;56(3):106114. doi:10.1016/j.ijantimicag.2020.106114

45. Hung IF-N, Lung K-C, Tso EY-K, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: An open-label, randomised, phase 2 trial. *The Lancet*. 2020;395(10238):1695-1704. doi:10.1016/s0140-6736(20)31042-4

46. Chien M, Anderson TK, Jockusch S, et al. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *J Proteome Res*. August 2020. doi:10.1021/acs.jproteome.0c00392

47. Sadeghi A, Ali Asgari A, Norouzi A, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): A randomized controlled trial. *Journal of Antimicrobial Chemotherapy*. August 2020. doi:10.1093/jac/dkaa334

48. Abbaspour Kasgari H, Moradi S, Shabani AM, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: A single-centre, randomized controlled trial. *Journal of Antimicrobial Chemotherapy*. August 2020. doi:10.1093/jac/dkaa332

49. Eslami G, Mousaviasl S, Radmanesh E, et al. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *Journal of Antimicrobial Chemotherapy*. August 2020. doi:10.1093/jac/dkaa331

50. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720-3732. doi:10.1182/blood-2010-07-273417

51. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: A retrospective cohort study. *The Lancet Rheumatology*. 2020;2(6):e325-e331. doi:10.1016/s2665-9913(20)30127-2

52. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: A cohort study. *The Lancet Rheumatology*. 2020;2(7):e393-e400. doi:10.1016/s2665-9913(20)30164-8

53. Cao X. COVID-19: Immunopathology and its implications for therapy. *Nat Rev Immunol*. 2020;20(5):269-270. doi:10.1038/s41577-020-0308-3

54. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *Journal of medical virology.n/a(n/a)*.

55. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020;117(20):10970-10975. doi:10.1073/pnas.2005615117

56. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. 2020;92(7):814-818.

57. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney International*. 2020;97(6):1083-1088. doi:10.1016/j.kint.2020.04.002

58. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: A retrospective cohort study. *The Lancet Rheumatology*. 2020;2(8):e474-e484. doi:10.1016/s2665-9913(20)30173-9

59. Strohbehn GW, Heiss BL, Rouhani SJ, et al. COVIDOSE: Low-dose tocilizumab in the treatment of Covid-19. *medRxiv*. July 2020. doi:10.1101/2020.07.20.20157503

60. Stebbing J, Phelan A, Griffin I, et al. COVID-19: Combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases*. 2020;20(4):400-402. doi:10.1016/s1473-3099(20)30132-8

61. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. *Journal of Infection*. 2020;81(2):318-356. doi:10.1016/j.jinf.2020.04.017

62. Walz L, Cohen AJ, Rebaza AP, et al. Janus Kinase-Inhibitor and Type I Interferon Ability to Produce Favorable Clinical Outcomes in COVID-19 Patients: A Systematic Review and Meta-Analysis. *medRxiv*. August 2020. doi:10.1101/2020.08.10.20172189

63. Haga S, Yamamoto N, Nakai-Murakami C, et al. Modulation of TNF- -converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-production and facilitates viral entry. *Proceedings of the National Academy of Sciences*. 2008;105(22):7809-7814. doi:10.1073/pnas.0711241105

64. Herold S, Hoegner K, Vadász I, et al. Inhaled granulocyte/macrophage colony-stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2014;189(5):609-611. doi:10.1164/rccm.201311-2041le

65. Bhattacharya P, Budnick I, Singh M, et al. Dual Role of GM-CSF as a Pro-Inflammatory and a Regulatory Cytokine: Implications for Immune Therapy. *Journal of Interferon & Cytokine Research*. 2015;35(8):585-599. doi:10.1089/jir.2014.0149

66. Presneill JJ, Harris T, Stewart AG, Cade JF, Wilson JW. A randomized phase II trial of granulocyte-macrophage colony-stimulating factor therapy in severe sepsis with respiratory dysfunction. *Am J Respir Crit Care Med*. 2002;166(2):138-143. doi:10.1164/rccm.2009005

67. Paine R III, Standiford TJ, Dechert RE, et al. A randomized trial of recombinant human granulocyte-macrophage colony stimulating factor for patients with acute lung injury. *Critical Care Medicine*. 2012;40(1):90-97. doi:10.1097/ccm.0b013e31822d7bf0

68. De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: A single-centre, prospective cohort study. *The Lancet Rheumatology*. 2020;2(8):e465-e473. doi:10.1016/s2665-9913(20)30170-3

69. Weinblatt ME, McInnes IB, Kremer JM, et al. A Randomized Phase IIb Study of Mavrilimumab and Golimumab in Rheumatoid Arthritis. *Arthritis Rheumatol*. 2018;70(1):49-59. doi:10.1002/art.40323

70. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: A preliminary study. *JAMA*. 2003;290(24):3222. doi:10.1001/jama.290.24.3222

71. Shalhoub S. Interferon beta-1b for COVID-19. *The Lancet*. 2020;395(10238):1670-1671. doi:10.1016/s0140-6736(20)31101-6

72. Zhou Q, Chen V, Shannon CP, et al. Interferon-$\alpha$2b Treatment for COVID-19. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.01061

73. Zhao Q, Ren H, Han Z. Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases. *Journal of Cellular Immunotherapy*. 2016;2(1):3-20. doi:10.1016/j.jocit.2014.12.001

74. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. *Aging and disease*. 2020;11(2):216. doi:10.14336/ad.2020.0228

75. Liang B, Chen J, Li T, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. *Medicine*. 2020;99(31):e21429. doi:10.1097/md.0000000000021429

76. Metcalfe SM. Mesenchymal stem cells and management of COVID-19 pneumonia. *Medicine in Drug Discovery*. 2020;5:100019. doi:10.1016/j.medidd.2020.100019

77. Zeiser R. Immune modulatory effects of statins. *Immunology*. 2018;154(1):69-75. doi:10.1111/imm.12902

78. Lima Martínez MM, Contreras MA, Marín W, D'Marco L. Estatinas en COVID-19: ¿existe algún fundamento? *Clínica e Investigación en Arteriosclerosis*. July 2020. doi:10.1016/j.arteri.2020.06.003

79. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *N Engl J Med*. 2020;382(25):e102. doi:10.1056/nejmoa2007621

80. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. 2020;40(5):998-1004. doi:10.1111/liv.14435

81. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. *Journal of Clinical Investigation*. 2020;130(4):1545-1548. doi:10.1172/jci138003

82. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *Journal of Clinical Investigation*. 2020;130(6):2757-2765. doi:10.1172/jci138745

83. Rojas M, Rodríguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: Possible mechanisms of action. *Autoimmunity Reviews*. 2020;19(7):102554. doi:10.1016/j.autrev.2020.102554

84. Nellis R. Convalescent plasma associated with reduced COVID-19 mortality in 35,000-plus hospitalized patients. https://newsnetwork.mayoclinic.org/discussion/convalescent-plasma-associated-with-reduced-covid-19-mortality-in-35000-plus-hospitalized-patients/.

85. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(5):1-11. doi:10.1001/jama.2020.10044

86. Mohtadi N, Ghaysouri A, Shirazi S, et al. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: A case series. *Virology*. 2020;548:1-5. doi:10.1016/j.virol.2020.05.006

87. Pourahmad R, Moazzami B, Rezaei N. Efficacy of Plasmapheresis and Immunoglobulin Replacement Therapy (IVIG) on Patients with COVID-19. *SN Compr Clin Med*. 2020;2(9):1407-1411. doi:10.1007/s42399-020-00438-2

88. Basu-Ray I, Almaddah N, Adeboye A, Soos MP. *Cardiac Manifestations Of Coronavirus (COVID-19)*. Treasure Island (FL): StatPearls; 2020.

89. Burzynski LC, Humphry M, Pyrillou K, et al. The Coagulation and Immune Systems Are Directly Linked through the Activation of Interleukin-1 $\alpha$ by Thrombin. *Immunity*. 2019;50(4):1033-1042.e6. doi:10.1016/j.immuni.2019.03.003

90. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847. doi:10.1111/jth.14768

91. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. doi:10.1111/jth.14817

92. Zhai Z, Li C, Chen Y, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. *Thromb Haemost*. 2020;120(06):937-948. doi:10.1055/s-0040-1710019

93. Hasan SS, Radford S, Kow CS, Zaidi STR. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: A systematic review and meta-analysis. *J Thromb Thrombolysis*. August 2020. doi:10.1007/s11239-020-02235-z

94. Arachchillage DJ, Remmington C, Rosenberg A, et al. Anticoagulation with argatroban in patients with acute antithrombin deficiency in severe COVID - 19. *Br J Haematol*. June 2020. doi:10.1111/bjh.16927

95. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. *The Lancet Respiratory Medicine*. 2020;8(5):506-517. doi:10.1016/s2213-2600(20)30161-2

96. Parikh R, Wilson C, Weinberg J, Gavin D, Murphy J, Reardon CC. Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients. *Ther Adv Respir Dis*. 2020;14:175346662093351. doi:10.1177/1753466620933510

97. Ferrari M, Santini A, Protti A, et al. Inhaled nitric oxide in mechanically ventilated patients with COVID-19. *Journal of Critical Care*. 2020;60:159-160. doi:10.1016/j.jcrc.2020.08.007

98. Karam O, Gebistorf F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: A Cochrane Systematic Review with trial sequential analysis. *Anaesthesia*. 2017;72(1):106-117. doi:10.1111/anae.13628

99. Isidori AM, Giannetta E, Pofi R, et al. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. *The DEDALO project Andrology.n/a(n/a)*.

100. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L. Selective regulation of cytokine secretion by hydroxychloroquine: Inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. *The Journal of rheumatology*. 1993;20(5):803-808.

101. van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *The Journal of rheumatology*. 1997;24(1):55-60.

102. Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Res Ther*. 2012;14(3):R155. doi:10.1186/ar3895

103. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*. 2020;71(15):732-739. doi:10.1093/cid/ciaa237

104. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BST*. 2020;14(1):72-73. doi:10.5582/bst.2020.01047

105. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949

106. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;382(25):2411-2418. doi:10.1056/nejmoa2012410

107. Health NIo. NIH Halts Clinical Trial of Hydroxychloroquine. https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine. Accessed August 31, 2020.

108. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. 2020;383(6):517-525.

109. Schögler A, Kopf BS, Edwards MR, et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. *Eur Respir J*. 2015;45(2):428-439. doi:10.1183/09031936.00102014

110. Lee N, Wong C-K, Chan MCW, et al. Anti-inflammatory effects of adjunctive macrolide treatment in adults hospitalized with influenza: A randomized controlled trial. *Antiviral Research*. 2017;144:48-56. doi:10.1016/j.antiviral.2017.05.008

111. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19. *Med*. June 2020. doi:10.1016/j.medj.2020.06.001

112. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open*. 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857

113. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *The Lancet*.

114. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: A multinational registry analysis. *The Lancet*. 2020;395(10240):1820. doi:10.1016/s0140-6736(20)31324-6

115. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Heart Outcomes Prevention Evaluation Study Investigators Lancet*. 2000;355(9200):253-259.

116. Velavan TP, Meyer CG. The COVID - 19 epidemic. *Trop Med Int Health*. 2020;25(3):278-280. doi:10.1111/tmi.13383

117. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: A peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacology & Therapeutics*. 2010;128(1):119-128. doi:10.1016/j.pharmthera.2010.06.003

118. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;111(20):2605-2610. doi:10.1161/circulationaha.104.510461

119. Ferrario CM, Jessup J, Gallagher PE, et al. Effects of renin-angiotensin system blockade on renal angiotensin-(1-7) forming enzymes and receptors. *Kidney International*. 2005;68(5):2189-2196. doi:10.1111/j.1523-1755.2005.00675.x

120. Mancia G, Rea F. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. 2020;382(25):2431-2440.

121. de Abajo FJ, Rodríguez-Martín S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: A case-population study. *The Lancet*. 2020;395(10238):1705-1714. doi:10.1016/s0140-6736(20)31030-8

122. Baral R, White M, Vassiliou VS. Effect of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-19: A Systematic Review and Meta-analysis of 28,872 Patients. *Curr Atheroscler Rep*. 2020;22(10):61. doi:10.1007/s11883-020-00880-6

123. Xia S, Lan Q, Su S, et al. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. *Sig Transduct Target Ther*. 2020;5(1):92. doi:10.1038/s41392-020-0184-0

124. Zhou Y, Vedantham P, Lu K, et al. Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Research*. 2015;116:76-84. doi:10.1016/j.antiviral.2015.01.011

125. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat Mesylate Blocks Activation of SARS-CoV-2: New Treatment Option for COVID-19. *Antimicrob Agents Chemother*. 2020;64(6). doi:10.1128/aac.00754-20

126. Lucas JM, Heinlein C, Kim T, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. *Cancer Discovery*. 2014;4(11):1310-1325. doi:10.1158/2159-8290.cd-13-1010

127. Ansarin K, Tolouian R, Ardalan M, et al. Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: A randomized clinical trial. *Bioimpacts*. 2020;10(4):209-215. doi:10.34172/bi.2020.27

128. Jin Z, Du X, Xu Y. Structure of M(pro) from SARS-CoV-2 and discovery of its inhibitors. 2020;582(7811):289-293.

129. Vuong W, Khan MB. Feline coronavirus drug inhibits the main protease of SARS-CoV-2 and blocks virus replication. 2020;11(1):4282.

130. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research*. 2020;178:104787. doi:10.1016/j.antiviral.2020.104787

131. Cao J, Forrest JC, Zhang X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Research*. 2015;114:1-10. doi:10.1016/j.antiviral.2014.11.010

132. Jasenosky LD, Cadena C, Mire CE, et al. The FDA-Approved Oral Drug Nitazoxanide Amplifies Host Antiviral Responses and Inhibits Ebola Virus. *iScience*. 2019;19:1279-1290. doi:10.1016/j.isci.2019.07.003

133. Korba BE, Montero AB, Farrar K, et al. Nitazoxanide, tizoxanide and other thiazolides are potent inhibitors of hepatitis B virus and hepatitis C virus replication. *Antiviral Research*. 2008;77(1):56-63. doi:10.1016/j.antiviral.2007.08.005

134. Rossignol J-F. Nitazoxanide: A first-in-class broad-spectrum antiviral agent. *Antiviral Research*. 2014;110:94-103. doi:10.1016/j.antiviral.2014.07.014

135. Rossignol J-F, Keeffe EB. Thiazolides: A new class of drugs for the treatment of chronic hepatitis B and C. *Future Microbiology*. 2008;3(5):539-545. doi:10.2217/17460913.3.5.539

136. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0

137. Clerici M, Trabattoni D, Pacei M, Biasin M, Rossignol J-F. The anti-infective Nitazoxanide shows strong immumodulating effects (155.21. *The Journal of Immunology*. 2011;186(1 Supplement):155.

138. Miner K, Labitzke K, Liu B, et al. Drug Repurposing: The Anthelmintics Niclosamide and Nitazoxanide Are Potent TMEM16A Antagonists That Fully Bronchodilate Airways. *Front Pharmacol*. 2019;10:51. doi:10.3389/fphar.2019.00051

139. Maldonado V, Loza-Mejía MA, Chávez-Alderete J. Repositioning of pentoxifylline as an immunomodulator and regulator of the renin-angiotensin system in the treatment of COVID-19. *Medical Hypotheses*. 2020;144:109988. doi:10.1016/j.mehy.2020.109988

140. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. *Medical Hypotheses*. 2020;144:110005. doi:10.1016/j.mehy.2020.110005

141. Li C, Han R, Kang L, et al. Pirfenidone controls the feedback loop of the AT1R/p38 MAPK/renin-angiotensin system axis by regulating liver X receptor-$\alpha$ in myocardial infarction-induced cardiac fibrosis. *Sci Rep*. 2017;7(1). doi:10.1038/srep40523

142. Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D3 level is associated with increased risk of COVID-19 infection: An Israeli population-based study. July 2020. doi:10.1101/2020.07.01.20144329

143. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. *medRxiv*. July 2020. doi:10.1101/2020.07.15.20151852

144. Patel NA DSS, Grainger DW, Mehra RM. Usefulness of Ivermectin in COVID-19 Illness 2020. 2020. https://www.isglobal.org/documents/10179/6022921/Patel+et+al.+2020+version+2.pdf/adf390e0-7099-4c70-91d0-e0f7a0b69e14. Accessed September 16, 2020.

145. Xu J, Zhang Y. Traditional Chinese Medicine treatment of COVID-19. *Complement Ther Clin Pract*. 2020;39:101165. doi:10.1016/j.ctcp.2020.101165

146. Ye Y. Guideline-based Chinese herbal medicine treatment plus standard care for severe coronavirus disease 2019 (G-CHAMPS): Evidence from China. 2020(2020).

147. Sharma S, Basu S, Shetti NP, Aminabhavi TM. Current treatment protocol for COVID-19 in India. *Sensors International*. 2020;1:100013. doi:10.1016/j.sintl.2020.100013

148. Nandan A, Tiwari S, Sharma V. Exploring alternative medicine options for the prevention or treatment of coronavirus disease 2019 (COVID-19)- A systematic scoping review. *medRxiv*. May 2020. doi:10.1101/2020.05.14.20101352

149. Nordling L. Unproven herbal remedy against COVID-19 could fuel drug-resistant malaria, scientists warn. *Science*. May 2020. doi:10.1126/science.abc6665

150. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *The Lancet Infectious Diseases*. 2020;20(10):1118. doi:10.1016/s1473-3099(20)30296-6

151. ASCOT. AustralaSian COVID-19 Trial. 2020. https://www.ascot-trial.edu.au/. Accessed September 21, 2020.

152. Network B. AustralaSian COVID-19 Trial (ASCOT) removes hydroxychloroquine and lopinavir/ritonavir arms of the trial. 2020. https://biomelbourne.org/australasian-covid-19-trial-ascot-removes-hydroxychloroquine-and-lopinavir-ritonavir-arms-of-the-trial/. Accessed September 21, 2020.

153. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *Jama*. 2020;323(18):1824-1836.