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# Pharmacotherapeutics for the Management of Coronavirus Disease 2019 (COVID-19): An Appraisal

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## I. Introduction

The COVID-19 pandemic caused by the novel coronavirus (SARS-CoV-2) continues to reshape the globe. Approximately 210 countries and territories worldwide have been affected by the COVID-19 disease. Pharmaceutical industries across the world are extremely engaged in developing treatments and vaccines for the highly contagious coronavirus that has killed over 377,584 people worldwide, infected more than 6.3 million and ravaged economies globally. No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxaemic respiratory failure, acute respiratory distress syndrome, and multiorgan failure that necessitates ventilatory support, often for several weeks.[1]At least half of patients with coronavirus disease 2019 (COVID-19) requiring invasive mechanical ventilation have died in hospital,and the associated burden on health-care systems, especially intensive care units, has been overwhelming in several affected countries.[2] Gastrointestinal and hepatic manifestations are common in COVID-19 infection. Gastrointestinal symptoms are not usually associated with severe disease whereas liver injury at presentation i.e. abnormality of atleast one of the liver enzymes is associated with significantly increased risk of death or ICU admission. This was revealed in a study from New York and was published in Gasteroenterology, May 2020.

**Clinical Trials and Therapeutics Underway**

Although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 *in vitro*, [3,4]at present there are no antiviral therapies of proven effectiveness in treating severely ill patients with COVID-19. A multicentre, open-label, randomised controlled trial (RCT) of hydroxychloroquine involving 150 adults admitted to hospital for COVID-19 reported no significant effect of the drug on accelerating viral clearance.[5] An RCT enrolling patients within 12 days of symptom onset found that favipiravir was superior to arbidol in terms of the clinical recovery rate at day 7 in patients with mild illness (62 [56%] of 111 with arbidol vs 70 [71%] of 98 with favipiravir), but not in those with critical illness (0 vs 1 [6%]).[6] In severe illness, one uncontrolled study of five patients given convalescent plasma suggested a possible benefit, although the patients already had detectable anti-SARS-CoV-2 neutralising antibodies before receipt of the plasma.[7]

An open-label RCT of oral **lopinavir–ritonavir** found no significant effect on the primary outcome measure of time to clinical improvement and no evidence of reduction in viral RNA titres compared to control.[8]However, per-protocol analyses suggested possible reductions in time to clinical improvement (difference of 1 day), particularly in those treated within 12 days of symptom onset. Further studies of lopinavir–ritonavir and other drugs are ongoing.

**Remdesivir** is a broad-spectrum antiviral medication developed by the biopharmaceutical company Gilead Sciences. As of 2020, remdesivir is being tested as a specific treatment for COVID-19, and has been authorized for emergency use in the U.S. and approved for use in Japan for people with severe symptoms. An investigator-initiated, individually randomised, placebo-controlled, double-blind trial was conducted to assess the effectiveness and safety of intravenous remdesivir in adults (aged ≥18 years) admitted to hospital with severe COVID-19. The trial was done at ten hospitals in Wuhan, Hubei, China) Patients received either intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the

same volume of placebo infusions for a total of 10 days (both provided by Gilead Sciences, Foster City, CA, USA). This dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. A higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped by the investigators because of adverse events including gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin increases, and worsened cardiopulmonary status. Ongoing studies with larger sample sizes will continue to inform our understanding of the effect of remdesivir on COVID-19.

Furthermore, strategies to enhance the antiviral potency of remdesivir (eg, higher-dose regimens, combination with other antivirals, or SARS-CoV-2 neutralising antibodies) and to mitigate immunopathological host responses contributing to COVID-19 severity (eg, inhibitors of IL-6, IL-1, or TNFα) require rigorous study in patients with severe COVID-19. Remdesivir did not result in significant reductions in SARS-CoV-2 RNA loads or detectability in upper respiratory tract or sputum specimens in this study despite showing strong antiviral effects in preclinical models of infection with coronaviruses. In one murine model of SARS, remdesivir treatment starting at 2 days after infection, after virus replication and lung airway epithelial damage had already peaked, significantly reduced SARS-CoV-1 lung titres but did not decrease disease severity or mortality. Remdesivir (also GS-5734) is a monophosphoramidateprodrug of an adenosine analogue that has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses.

In vitro, [9]remdesivir inhibits all human and animal coronaviruses tested to date, including SARS-CoV-2,and has shown antiviral and clinical effects in animal models of SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoVinfections.In a lethal murine model of MERS, remdesivir was superior to a regimen of combined interferon beta and lopinavir–ritonavir.[10] Remdesivir is a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells.In a non-lethal rhesus macaque model of SARS-CoV-2 infection, early remdesivir administration was shown to exert significant antiviral and clinical effects as evidenced by reduced pulmonary infiltrates and virus titres in bronchoalveolar lavages vs vehicle only. IV Remdesivir was studied for treatment of Ebola virus disease, in which it was adequately tolerated but found to be less efficacious than several monoclonal antibody therapeutics. IV Remdesivirhas been used on the basis of individual compassionate use over the past several months in patients with COVID-19 in some countries.[11]Many case studies have reported benefit in severely ill patients with COVID-19 but theclinical and antiviral efficacy of remdesivir in COVID-19 remains to be established.

The results of a placebo-controlled randomised trial of remdesivir in patients with severe COVID-19 have proved that intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo. The study was terminated before attaining the prespecified sample size. In the intention-to-treat population, the primary endpoint of time to clinical improvement was not significantly different between groups, but was numerically shorter in the remdesivir group than the control group, particularly in those treated within 10 days of symptom onset. The duration of invasive mechanical ventilation, although also not significantly different between groups, was numerically shorter in remdesivir recipients than placebo recipients.[12] Future studies of remdesivir, including earlier treatment in patients with COVID-19 and higher-dose regimens or in combination with other antivirals or SARS-CoV-2 neutralising antibodies in those with severe COVID-19 are needed to better understand its potential effectiveness.

**Ivermectin**is an FDA-approved broad spectrum anti-parasitic agent that in recent years we, along with other groups, have shown to have anti-viral activity against a broad range of viruses in vitro.Ivermectin is an inhibitor of the COVID-19 causative virus (SARS-CoV-2) in vitro. A single treatment is able to effect ~5000-fold reduction in virus at 48 h in cell culture. [13] Ivermectin is FDA-approved for parasitic infections, and therefore has a potential for repurposing. Ivermectin is widely available, due to its inclusion on the WHO model list of essential medicines. Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore warrants further investigation for possible benefits in humans.

The **4-aminoquinoline antimalarialschloroquine and hydroxychloroquine** have been promoted and sometimes used in the treatment of COVID-19, alone or combined with azithromycin, based on their immunomodulatory and antiviral properties, despite an absence of methodologically appropriate proof of their

efficacy. The global community awaits the results of ongoing, well powered randomised controlled trials showing the effects of chloroquine and hydroxychloroquine on COVID-19 clinical outcomes. These drugs, however, might be associated with cardiac toxicity. Macrolides1 and 4-aminoquinolines2 prolong ventricular repolarisation, as evidenced by QT interval prolongation corrected for heart rate (QTc) on the electrocardiogram. QTc prolongation can be associated with a specific ventricular arrhythmia called torsade de pointes, which, although often self-terminating, can degenerate into ventricular tachycardia or fibrillation, leading to death. Torsade de pointes is a rare event, with an estimated annual crude incidence of 3·2 per million population. The incidence is almost doubled in women compared with men and increases with age. Drug-induced torsade de pointes mostly occurs in the presence of several risk factors, including high drug concentration, simultaneous exposure to multiple QTc-prolonging drugs, coronary heart disease, heart failure, hypokalaemia, bradycardia, or congenital long-QT syndrome, among others.Hospitalised COVID-19 patients who are treated with chloroquine or hydroxychloroquine with or without an antibiotic are twice as likely to die compared to controls, who did not receive these agents. After controlling for age, sex, race or ethnicity, underlying comorbidities, and disease severity at baseline, the use of all four regimens was associated with an increased hazard for de-novo ventricular arrythmia and death in hospital. This study provides real-world evidence on the use of these therapeutic regimens by including a large number of patients from across the world. Therefore, these findings provide the most comprehensive evidence of the use of hydroxychloroquine and chloroquine (with or without a macrolide) for treatment of COVID-19.This fact was revealed in an analysis of 96000 patients from 671 hospitals in 6 continents. [14]

The **first COVID-19 vaccine** to reach phase 1 clinical trial is safe, well-tolerated, and capable of generating an immune response against the novel coronavirus in humans. The broad objective of the phase 1 trial was to assess the safety and ability of the new **Ad5-nCoV Vaccine** to generate an immune response of different dosages in healthy adults between the ages of 18-60 years. The trial subjects were assigned to receive a single injection of the vaccine in either low dose, middle dose, or high dose. Blood samples were drawn at regular intervals post-vaccination to record the development of antibodies as well as T cells. According to the study of 108 adults, the vaccine produced neutralizing antibodies, and a response mediated by the immune system's T-cells against the novel coronavirus, SARS-CoV-2 after 28 days with the final results to be evaluated in the time frame of 6 months. The Ad5 vectored COVID-19 vaccine is the first to be tested in humans. It uses a weakened common cold causing adenovirus which infects human cells readily, but is incapable of causing disease as well as inefficient in delivering genetic material that codes for the SARS-CoV-2 spike protein to the cells. These cells then produce the spike protein, and travel to the lymph nodes where the immune system produces antibodies which in turn recognize the spike protein and combats the coronavirus infection. The results of phase 1 clinical trial has set an important milestone to the extent that a single dose of the new adenovirus type 5 vectored COVID-19 (Ad5-nCoV) vaccine produces virus-specific antibodies and T cells in 14 days.

However, the scientists all over the world have the current opinion that further research is needed to confirm whether the vaccine protects against SARS-CoV-2 infection. As far as Serious Adverse Events (SAE) are concerned, they were mild to moderate in nature. At least 1 Adverse Drug Reaction (ADR) was reported with 83% of those receiving low and middle doses of the vaccine and 75% of those in the high dose group within 7 days vaccination. The ADRs noted were mild pain at the injection site in over 50% of the vaccine recipients, fever was noted in 50% of those with mild pain, followed by fatigue, headache, and myalgia. It was noted that all dose levels of the vaccine were capable of generating some level of immune response with 50% of the trial participants in low and middle dose groups and 75% of those in the high dose group exhibited neutralizing antibodies against SARS-CoV-2. A rapid T cell response was noted in majority of the trial participants. After 28 days following vaccination, most of the study subjects also revealed almost four fold increase in the binding antibodies. High level of pre-existing immunity to adenovirus type 5 which is the common cold virus vector used in the clinical trial might have reduced both the antibody and T-cell response in the form of rapid immune responses and peaking level of them in the trial participants. The study limitations were small sample size and short duration with lack of randomized control group.

A candidate drug for treating the new coronavirus, **Favipiravir**, has produced promising results in early clinical trials. This trial was funded by the Russian Direct Investment Fund. About 60% of the 40 coronavirus patients taking oral tablets of the drug favipiravir, which was first developed and approved in Japan as an anti-influenza (AVIGAN $^{TM}$), tested negative for the virus within five days and this drug treatment has been thought to curb the recovery times in half. Favipiravir is also undergoing trials in India by Glenmark Pharmaceuticals Ltd. The clinical trial of 330 patients infected with the coronavirus should be finished by the end of May 2020 as declared by the chairman of the board of directors at ChemRar, the pharmaceutical company conducting the trials. On June 20, Glenmark Pharmaceuticals launched Favipiravir (FAVIFLU) for the treatment of patients with mild to moderate COVID-19 symptoms.

**Galidesivir**, abroad spectrum anti-viral drug is an adenosine nucleoside analogue that acts to block viral RNA polymerase. It was developed by BioCryst Pharmaceuticals for the treatment of hepatitis C, and developed for the treatment of deadly filovirus infections like Ebola virus, Yellow Fever, and Marburg virus. It is in advanced development for the treatment of COVID-19. A randomized double-blind, placebo-controlled clinical trial to assess the safety clinical impact and antiviral effects of galidesivir in patients with COVID-19is undergoing. The trial (NCT03891420) is being funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.Galidesivir has been safe and well tolerated in Phase 1 studies that was reported previously. This drug has demonstrated broad-spectrum activity in-vitro against more than 20 RNA viruses in nine different families, including the coronaviruses that cause MERS and SARS, filoviruses, togaviruses, bunyaviruses, arenaviruses, paramyxoviruses, and flaviviruses. In the COVID-19 trial, efficacy measures include time to clinical improvement, time to hospital discharge, time to undetectable levels as measured by PCR in respiratory specimens of SARS-CoV-2, and all-cause mortality. There are two parts of the ongoing clinical trial. Part 1 of the trial has enrolled 24 hospitalized adults diagnosed with moderate to severe COVID-19 confirmed by PCR. Then three cohorts of eight patients were randomized to receive IV Galidesivir (n=6) or Placebo (n=2) every 12 hours for total duration of 7 days. Upon completion, an optimized dosing regimen would be chosen for part 2 of the trial based upon the results related to safety, viral load reduction in respiratory tract secretions, improvement in COVID-19 signs and symptoms and clinical features, and mortality. Upto 42 hospitalized patients would be randomized 2:1 to receive IV Galidesivir or Placebo. After completion of treatment, all the trial subjects would remain hospitalized until resolution of symptoms and subxequently followed up for mortality through day 56.

Clinical trial data on the efficacy and safety of **traditional Chinese Medicine (TCM) LianhuaQingwen (LH)** which is a repurposed Chinese herb in capsules is manufactured by Yiling Pharmaceutical in China. When tested on COVID-19 patients, it has been revealed that the capsules can apparently relieve symptomsand increase the cure rate of patients with mild symptoms. Sample size of the trial was 284 COVID-19 patients who were then equally assigned to two arms: one receiving LH capsules and the other without LH capsules. According to the results of this trial, the resolution rate of chief clinical symptoms i.e. fever, fatigue, and cough reached 57.7% on day 7 of treatment, 80.3% on day 10, and 91.5% on day 14. Comparative analysis has shown that treatment with LH capsules for a total duration of 14 days resulted in a significantly higher rate and a shorter time of symptom recovery than the control group not receiving LH capsules. [15] LH is a TCM containing 13 herbs, including Lonicera japonica, Forsythia suspense and Rhodiolarosea. This polyherbal formulation has been marketed since the SARS crisis in 2003 in China and then widely used in the country to treat SARS, H1N1, and COVID-19. Interestimg fact is that Lonicera japonica and Forsythia suspense block the binding of COVID-19 with human blood vessels, and Rhodiolarosea inhibits the acute inflammatory reaction in the pulmonary tissue. Thus TCM can improve clinical symptoms of COVID-19 but cannot cure or kill the novel coronavirus by direct mechanism.

A clinical trial sponsored by Inserm in France has been started in order to evaluate and compare some of the therapeutic combinations: **Remdesivir, lopinavir, the lopinavir+interferon combination, each combined with standard of care** that primarily consist of symptomatic treatments, and finally standard of care alone. This is an "adaptive" clinical trial in which ineffective compounds will be abandoned and any that appear to be useful will be tested.

***Below listed are some of the various types of research projects as proposed by the researchers around the globe according to the need to explore the latest COVID-19 pandemic management:***

| **Theme of Project** | **Title of the Project** |
|---|---|
| Epidemiology | Mathematical modelling to anticipate risk of 2019-nCoV importation by geographical area<br>Monitoring of subjects with confirmed exposure to the novel 2019 coronavirus through virology and immunology studies. |
| Diagnostic, clinical, and therapeutic research | Identification and characterization of human monoclonal antibodies neutralizing 2019-nCoV with the potential for development towards vaccine candidates<br>Randomized, multicenter, adaptive study of the efficacy and safety of treatments for hospitalized patients presenting with COVID 2019 infection |
| Human and Social Sciences | Use of the Social Sciences to inform public policy in terms of communication in the event of an emerging epidemic, based on social media treatment of the 2019-nCoV epidemic<br>General population and healthcare professional knowledge, perceptions and behaviors in Metropolitan France in the face of the Covid-2019 epidemic |
| Fundamental Research | Role of furins in SARS-CoV-2 Spike protein maturation: evaluation of the antiviral potential of furin inhibitors<br>Proof of Concept for the rapid production of recombinant SARS-CoV-2 |

| | |
|---|---|
| | Implementation of an experimental model of SARS-CoV-2 infection in the cynomolgus monkey |

Clinical trials getting underway in Australia and Europe are testing the effectiveness of **BCG vaccination** for reducing the prevalence and severity of COVID-19 symptoms in high-risk populations such as health care workers (HCW) and the elderly as reported by Reuters Health. Several other antiviral drugs are being investigated with activity against various influenza subtypes, HCV, and HIV viruses. These include umifenovir (ARBIDOL), triazavirin (TZV), and baloxavirmarboxil (XOFLUZA), danoprevir/ritonavir, darunavir/cobicistat, sofosbuvir/ledipasvir etc. There is evidence that a hyperinflammatory response significantly significantly contributes to mortality in COVID-19 infections. [16]

Trials with **Corticosteroids** were inconclusive with greater adverse effects. There are seven registered trials with the anti-IL-6 drug tocilizumab. Other immunosuppressants under investigation are adalimumab (anti-TNF), eculizumab (anti-C5), sarilumab (anti-IL-6), ixekizumab (anti-17A), and fingolimod (sphingosine-1-phosphate receptor modulator for multiple sclerosis). Meplazumab (anti-CD-17) is an inhibitor of Tcellchemotaxis and virus cell entry and has proved to possess improved clinical and virological outcomes.[17]

Conversely, several studies are investigating immune stimulation. These include **the anti-PD-1 antibody camrelizumab, recombinant IL-2, CSA0001** (LL-37 antiviral peptide with immunomodulatory functions), **CD24FC** [fusion protein that prevents Toll-like receptor (TLR) activation and activates immunosuppressive Siglecsignalling] and recombinant human granulocyte colony-stimulating factor (rhG-CSF). Three further studies are investigating nonpharmaceutical interventions to modulate the immune system using cytokine filtration devices, such as oXiris and CytoSorb, to reduce circulating cytokines and inflammatory mediators. Twenty-four registered studies plan to investigate the role of **mesenchymal stem cells (MSCs)**. MSCs have immunomodulatory and tissue repair effects through the secretion of cytokines and growth factors. They have previously been examined in a Phase I trial in Adult Respiratory Distress Syndrome (ARDS). [18] Given that most of the deaths in COVID-19 are from respiratory failure, MSCs are postulated to have a beneficial effect.[19]

Use of **plasma** from patients who have recovered from COVID-19 has the potential benefit of providing disease-specific neutralising antibodies, before targeted therapies can be developed. During the Ebola outbreak in 2014, the WHO advised the use of convalescent plasma or whole-blood therapies.There are currently 12 registered trials to investigate **convalescent plasma or immunoglobulins** in COVID-19.Currently, six studies are looking at the use of antivirals, such as **umifenovir, antimalarials, such as hydroxychloroquine and chloroquine, and the use of recombinant human interferon alpha (a)1b spray** for the prevention of infection.Various other treatment strategies are currently under investigation, including the antifibrotic/inflammatory agent pirfenidone (used in treatment of idiopathic pulmonary fibrosis), and the antiangiogenic agents: bevacizumab (anti-VEGF) and thalidomide.

Thirty-five trials are now investigating the use of the antimalarial drugs chloroquine and hydroxychloroquine against COVID-19. Chloroquine was found to have significant inhibitory effects on viral cell entry and replication in vitro. [20] An early report of clinical experience in 100 patients with COVID-19 reported both beneficial clinical and virological outcomes with chloroquine treatment. [21] More recently, a non-randomised open-label study examining the effect of hydroxychloroquine (EU Clinical Trial Numbervii: 2020-000890-25; recruitment target stated as 25 participants in the registry) reported on a cohort of 36 patients. [22] It reported a significant reduction in nasopharyngeal swab viral positivity 6 days after inclusion in the hydroxychloroquine group compared with control. However, in a deviation from their registry-described protocol, 16 patients were designated as controls and six patients received concurrent treatment with azithromycin to prevent bacterial superinfection. Selection of patients receiving azithromycin was based on clinical judgement. The subgroup receiving azithromycin all had negative viral swabs after 6 days compared with 57% (8/14) of hydroxychloroquine alone and 12.5% (2/16) of control.This study is limited by its lack of randomisation and blinding, and small sample size. There is much interest in chloroquine or hydroxychloroquine for the treatment of COVID-19, with a further 34 studies registered. However, only four report using a robust double-blind randomised controlled protocol to investigate efficacy.

The Solidarity Trial is an international clinical trial to help find an effective treatment for COVID-19, launched by WHO and partners. It is hoped that one or more of the treatments under trial will result in improving clinical outcomes in COVID-19 patients and save lives. The treatment options are: Remdesivir; Lopinavir/Ritonavir; and Lopinavir/Ritonavir with Interferon beta-1a. The treatment options were originally selected based on evidence from laboratory, animal and clinical studies.As per the initial trial protocol, chloroquine and hydroxychloroquine had both been selected as potential drugs to be tested within the Solidarity Trial. However the trial was only ever pursued with hydroxychloroquine. On 17 June 2020, WHO announced

that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment was being stopped.The U.K. government authorised the State-funded National Health Service (NHS) to use steroid, the world's first coronavirus treatment proven to reduce the risk of death among severely ill patients. The drug has been proven to reduce the risk of death significantly in COVID-19 patients on ventilation by as much as 35% and patients on oxygen by 20%.

## II. Conclusion

To summarise, the outbreak of highly infectious and contagious coronavirus disease 2019 has heralded the necessity to begin research on the overall management of this emergency situation in different countries across the world. Nevertheless, vaccine development and clinical trials of such vaccines may enlighten the need to implement them immediately in the vulnerable population so far we are concerned about the critical and unpredictable course of the disease. The global impact of this new epidemic is still uncertain. Various drugs have shown their beneficial effects in vitro as well as in vivo while many of the chemical compounds have been explored and taregeted to alleviate the notorious coronavirus disease outcome in terms of morbidity and mortality. Future studies are of utmost importance to study the diverse aspects of this viral disease.

**Compliance with Ethical Standards**

Conflict of Interest – None

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