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# TRENDS IN COVID-19 THERAPEUTIC MODALITIES: A NARRATIVE LITERATURE REVIEW ARTICLE

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## ABSTRACT

As of 25 April 2020, the World Health Organization reports a total of 2,828,772 cases of 2019-nCoV infection and 197,924 deaths. No definite therapeutic agents or vaccines for COVID-19 are existing. Several therapies, such as remdesivir, ribavirin, and favipiravir, are under investigation and clinical trial. The use of convalescent plasma was recommended as an empirical treatment during outbreaks of the Ebola virus. While the production of vaccines and biotherapies that primarily target SARS-CoV-2 is necessary, the origination of drugs and biological medication can last between months to years, meaning it incapable of benefiting currently infected patients. Accelerated response to this pandemic would be significantly helped by the opportunity to repurpose old medications as novel antiviral medications. This review pays particular attention to the potential of repurposing already existing compounds that may offer new chances for managing people infected with SARS-CoV-2.

**KEWWORDS:** COVID-19; SARS-CoV-2; Coronavirus; Treatments.

## INTRODUCTION

Coronaviruses are life-threatening human and animal pathogens. In December of 2019, a novel new coronavirus was recognized as the reason for pneumonia cases in Wuhan, a city in the Hubei Province of China. It quickly spread, causing an epidemic everywhere in China, followed by a growing number of cases in other countries over the world (Martinez, 2020). In February 2020, the WHO named the disease COVID-19, which stands for coronavirus disease in 2019. The virus that rises COVID-19 is nominated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); formerly, it was referred to as 2019-nCoV (WHO, 2020).

SARS-CoV-2 is a new human betacoronavirus. Coronavirus is an enveloped, non-segmented, RNA virus. Their surface possesses club-shaped protrusions made by trimers of the spike (S) protein. The early engagement of the virion to the host cell is started by interactions between the S-protein and its receptor, which differs according to the specific virus (Fehr and Perlman, 2015). The S-protein/receptor is the primary component for the virus to infect a host and control the tissue tropism of the virus. Infectivity assays have proven that 2019-nCoV uses the angiotensin-converting enzyme 2 (ACE2) for entrance into infected cells, like SARS-CoV (whose genome is > 99.9% similar) (Chan et al., 2020).

While the evolution of vaccines and biotherapies that primarily target SARS-CoV-2 is essential, the origination of drugs and biological medication can last between months to years, meaning it incapable of benefiting currently infected patients. The optimum strategy to treat COVID-19 is uncertain. There are no remedies that have recognized effective; for most potential treatments, proof for their use comes predominantly from observational case series and circumstantial use based on in vitro or extrapolated indirect evidence. It is essential to admit that no well-controlled data are supporting the use of any of these medications, and their effectiveness and safety for COVID-19 are largely indefinite.

This review pays particular attention to the potential of repurposing already existing compounds that may offer new chances for managing people infected with SARS-CoV-2. Preceding work with SARS-CoV and MERS-CoV has provided a way to quicken the identification of significative therapies for fighting the novel new SARS-CoV-2 epidemic. Below are alphabetically listed medications with possible or promising efficacy.

### Identification of the literature

We searched the PubMed and EMBASE database till April 25, 2020, using keywords amiodarone, azithromycin, chloroquine, convalescent plasma, favipiravir, hydroxychloroquine, interferons, intravenous immunoglobulin, ivermectin, lopinavir-ritonavir, oseltamivir, paramivir, zanamivir, ganciclovir, acyclovir,

remdesivir, ribavirin, tocilizumab, SARS-CoV-2, and COVID-19. Only literatures written in English were included, articles that were written in Chinese or any other languages were excluded. We also retrieved the currently ongoing trials from Clinical Trials.gov. Inconsistencies and doubts around the relevance of the sources were solved by consensus between authors.

**Amiodarone**

Amiodarone demonstrated the ability to block the spreading of SARS CoV infection in cell cultures with no modification in the density of ACE2 receptors on the cell surface or interfering with the attachment of SARS-CoV to the cells (Aimo et al., 2020). Remarkably, amiodarone showed antiviral effect even if SARS-CoV could distribute its genome within the cytoplasm through the plasma membrane, thus avoiding the endocytic chamber (Aimo et al., 2020). Hence, though the antiviral activity of amiodarone is most likely due to interference with the endocytic pathway (Figure 1), additional mechanisms cannot be excluded. Amiodarone prevents hepatitis C virus infection by downregulating the CD81 receptor, but inhibition of virus assembly and release has also been proposed (Cheng et al., 2013).

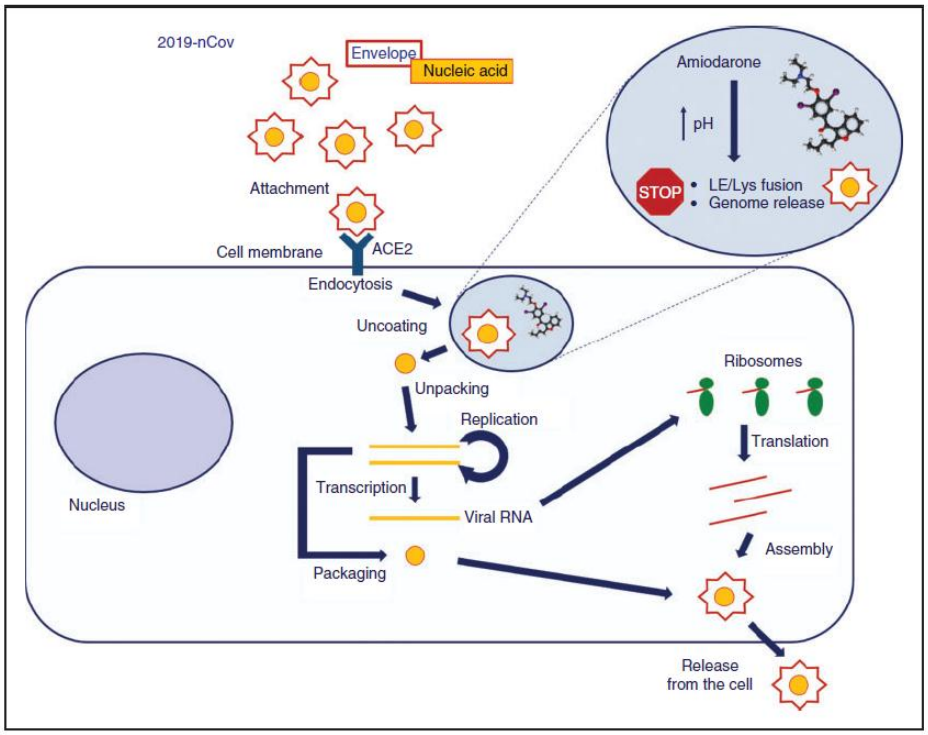


**Figure 1: The suggested mechanism of action of Amiodarone on Coronavirus replication.**

**Azithromycin**

Azithromycin has been discovered in 1980 an antibiotic in the macrolide class, with activity against a broad spectrum of microorganisms, a favorable side effect profile, and long half-life, it provided a therapeutic option for clinical conditions including upper respiratory tract infections enteric, and genitourinary bacterial infections (Kaldor and Steer, 2019). It is not approved for the treatment of viral infections (Damle et al., 2020). one study recommended the use of azithromycin in conjugation with hydroxychloroquine and was associated with more rapid resolution of virus detection than hydroxychloroquine alone or in relation to the control group Figure 2. (Gautret et al., 2020). Another observational study found no proof of a strong antiviral benefit or clinical efficacy of the combination of hydroxychloroquine and azithromycin for the treatment of patients with COVID-19 severely ill (Molina et al., 2020). Both hydroxychloroquine and azithromycin are associated with QTc prolongation, and use in combination may aggravate this adverse effect. Patients getting this regimen necessitate, at a minimum, serial electrocardiograms, Besides, many of these patients already have cardiac diseases, including arrhythmias. In a case report of 72 years old female, her baseline showed sinus rhythm with an interventricular conduction delay with a QRS duration of 128 ms and a QTc of 458 ms after her diagnosing with COVID-19 and starting on the hydroxychloroquine with azithromycin regimen after the patient had received 1 dose, a repeat ECG showed a QRS and QTc duration of 160 ms and 472 ms respectively. On the following day the QRSd and QTc, were 160 ms and 520 ms, respectively. Figure 3.(Gabriels et al., 2020).

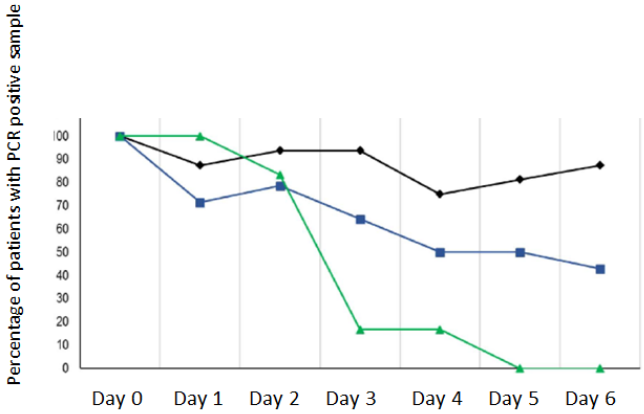


**Figure 2: Percentage of patients with PCR-positive samples from inclusion to day 6 treated with hydroxychloroquine only (blue line), treated with hydroxychloroquine and azithromycin combination (green line), and in COVID-19 control patients (black line).**

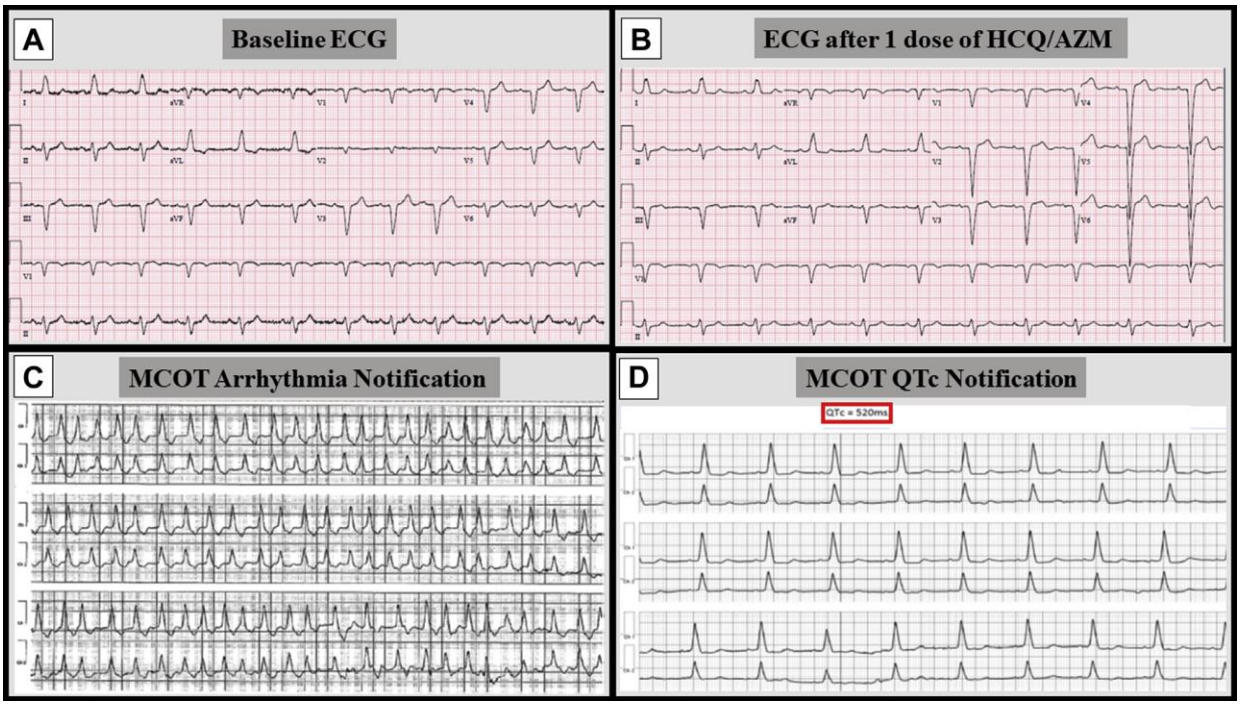


**Figure 3: Electrocardiograms recordings from a patient with COVID-19 treated with hydroxychloroquine and azithromycin. A: Baseline ECG, QRS duration: 128 ms, QTc: 458 ms. B: ECG after 1 dose, QRSd: 160 ms, QTc: 472 ms. C: Notification from mobile continuous telemetry (MCOT). D: Notification from MCOT with QTc measurement (520 ms).**

**Chloroquine**

Chloroquine phosphate, an old widely-used cheap drug for the treatment of malaria and autoimmune disease, recently shown a potential broad-spectrum antiviral drug (Savarino et al., 2006, Yan et al., 2013) with efficacy and acceptable safety against COVID-19 related pneumonia in clinical trials conducted in China (Gao et al., 2020). Chloroquine is recognized to block virus infection by elevating endosomal pH required for virus/cell fusion, and by interference with the glycosylation of cellular receptors of SARS-CoV (Vincent et al., 2005, Yang et al., 2004). The fact that chloroquine has a significant inhibitory effect for viral replication while the susceptible cells managed either before or after infection proposes a possible prophylactic and therapeutic use (Keyaerts et al., 2004). It was a very effective option in reducing viral replication, offer an effective concentration of 6.90 µM that can be easily attainable with standard dosing, owing to its favorable penetration in the lung (Cortegiani et al., 2020). In a new publication, Gao and colleagues declared that results from more than 100 patients have confirmed that chloroquine is superior to the control treatment in managing the exacerbation of pneumonia, improving lung imaging findings, and shortening the disease course(Gao et al., 2020). Dosing for patient ≥50 kg:

Oral: 1 g once on day one, followed by 500 mg daily for a total treatment duration of 4 to 7 days (FDA, 2020). Of note, chloroquine is considered to be safe, and side-effects are generally mild and transitory. Though the margin concerning the therapeutic and toxic dosage is narrow and chloroquine has been associated with cardiovascular disorders that can be life-threatening (Touret and de Lamballerie, 2020). Several precautions with chloroquine usage, including blood testing, to rule out the development of thrombocytopenia, anemia, or leukopenia as well as serum electrolytes disturbances or renal and hepatic dysfunction. Routine electrocardiography to rule out the progress of QT interval prolongation and bradycardia. Monitoring for the appearance of visual and mental deterioration (Cortegiani et al., 2020).

**Convalescent plasma**

for more than one-century convalescent plasma therapy, classic adoptive immunotherapy has been applied to the treatment and prevention of various infectious diseases. Over the past two decades, convalescent plasma therapy was effectively used in the management of SARS, MERS, and H1N1 with acceptable efficacy and safety (Ko et al., 2018, Hung et al., 2011). A meta-analysis from thirty-two studies of SARS coronavirus infection showed a statistical significant reduction in the mortality following convalescent plasma therapy, compared with no therapy (Mair-Jenkins et al., 2015). Because the clinical and the virological characteristics share similarity between SARS, MERS, and COVID-19 convalescent plasma therapy might be a hopeful treatment choice for COVID-19 rescue (Chen et al., 2020b). In a case series of five critically ill patients with confirmed COVID-19 and acute respiratory distress syndrome. All of them were treated with convalescent plasma. management with plasma containing antibodies showed improvement in their clinical status (Shen et al., 2020). A result from a pilot study enrolled ten severely ill patients with COVID-19 showed that the clinical symptoms were significantly improved besides the increase of oxyhemoglobin saturation within three days. Multiple other parameters tended to improve, including lymphocyte counts and decreased C-reactive protein. No severe adverse effects were detected. This study showed convalescent plasma therapy was well tolerated and might improve the clinical outcomes (Duan et al., 2020).

**Favipiravir**

A novel RNA-dependent RNA polymerase inhibitor prodrug, which is effective in the management of Ebola and influenza viruses (Sissoko et al., 2016, Furuta et al., 2013). Recent in vitro report showed that both favipiravir and remdesivir were effective in reducing the SARS-CoV-2 infection. This report highlighted favipiravir as a potential clinical intervention for COVID-19 (Wang et al., 2020b). a new open-label experimental treatment with favipiravir for COVID-19 favipiravir exhibited better therapeutic results in terms of disease progression and viral clearance (Sissoko et al., 2016).

**Hydroxychloroquine**

Hydroxychloroquine sulfate, a derivative of chloroquine, was first produced in 1946 by introducing a hydroxyl group into chloroquine and was proven to be much less (~40%) toxic than chloroquine in animals (McChesney, 1983). It is still widely available to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Since chloroquine and hydroxychloroquine share comparable chemical structures as a weak base and mechanisms of action as an immunomodulator, it is easy to conjure up the idea that HCQ may be a persuasive candidate to treat infection by SARS-CoV-. Hydroxychloroquine is a weak base that is recognized to increase the pH of acidic intracellular organelles, such as endosomes and lysosomes, needed for membrane fusion (Mauthe et al., 2018). The clinical analysis found that a high level of cytokines was identified in the plasma of critically ill patients infected with SARS-CoV-2, proposing that the cytokine storm was linked with disease severity (Huang et al., 2020). Other than hydroxychloroquine direct antiviral activity, it is a safe and effective anti-inflammatory agent; Therefore, in COVID-19 patients, hydroxychloroquine may also contribute to attenuating the inflammatory response (Liu et al., 2020a). Published clinical data are limited. In an open-label study of 36 adults with COVID-19, the use of hydroxychloroquine was related to a greater rate of undetectable SARS-CoV-2 RNA on nasopharyngeal specimens at day six compared with no specific treatment (Gautret et al., 2020). In a randomized trial of 30 infected patients with COVID-19 in Shanghai, the percentage of patients with nasopharyngeal viral clearance at day 7 was not significantly different with hydroxychloroquine (400 mg daily for 5 days) compared with standard of care, and 1 patient in the hydroxychloroquine arm developed the severe disease (Chen et al., 2020a).In the USA, the FDA has issued an emergency use authorization to allow the use of these agents in adolescents or adults hospitalized for COVID-19. At this time, no data available to support use for prophylaxis, even though studies are ongoing to evaluate the drug's role for postexposure prophylaxis for household contact and health care workers. Whenever possible, treatment should be given as part of a clinical trial. For optimum treatment, it may be necessary to administer a loading dose followed by a maintenance dose (Colson et al., 2020). Two dosing regimens are recently published : Oral: 400 mg twice daily on day 1, followed by 400 mg/day single dose or in 2 divided doses, for a total treatment duration of 5 days (Yao et al., 2020) **or** 800 mg once on day 1, followed by 400 mg/day single dose or in 2 divided doses, for a total treatment period of 4 to 7 days (Perinel et al., 2020).

**Interferons**

Type 1 interferons elect a group of cytokines including the ubiquitous α and β subtypes as well as the ε, ω, and κ subtypes (Samuel, 2001). They are released by various cell types, upon the identification of viral components (Liu, 2005). interferons are amongst the principal

cytokines produced during a viral infection. They inhibit viral replication and spread in several ways such as a slowdown of cell metabolism or secretion of cytokines which endorse the activation of adaptive immunity. a combination of interferon β with lopinavir/ritonavir against MERS-CoV enhanced pulmonary function but decreased virus replication was insignificant (Sheahan et al., 2020). Interferon β1 might offer a safe and easy to upscale treatment against COVID-19 in the initial stages of infection (Sallard et al., 2020). In fact, it had a mixed efficiency against MERS-CoV and SARS-CoV viruses, but in vitro studies proposed that SARS-CoV-2 could be substantially more sensitive to Type 1 interferon than other coronaviruses. Also be applicable to evaluate type III interferon for the treatment of COVID-19, because of the protective effects of this interferon in the respiratory tract Figure 4 (Lokugamage et al., 2020). the subcutaneous and intravenous modes of administration are both well-described, have already proven safe, and have similar pharmacokinetics and pharmacodynamics (Mager and Jusko, 2002). In China, the guidelines recommend administering 5 million U of IFNα by vapor inhalation twice daily to the patients, in combination with ribavirin (Dong et al., 2020, Lu, 2020). Interferons I treatment should be restricted to the initial phases of the infection (Siddiqi and Mehra, 2020) early clinical data showed that inflammatory biomarkers are related to the increased mortality (Zhou et al., 2020).

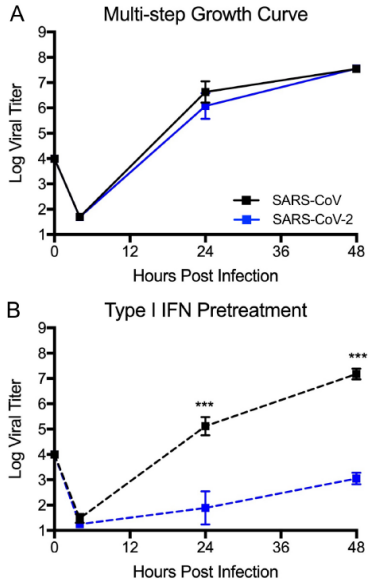


**Figure 4: SARS-CoV-2 sensitivity to type I IFN pretreatment.**
A) Vero E6 cells infected with either SARS-CoV (black) or SARS-CoV-2 (blue)
B) Vero E6 cells treated with recombinant type I IFN for 18 hours prior to infection.

**Intravenous Immunoglobulin**
Intravenous immunoglobulin (IVIg) therapy is commonly used to treat infectious and autoimmune disorders (Hori et al., 2020). In a report on 3 cases of COVID-19 who treated with high-dose intravenous (IVIg) 25 grams per day, they showed satisfactory clinical outcome and radiographic recovery. None of the three cases reported any adverse events (Cao et al., 2020b).

**Ivermectin**
Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent1 that recently, along with other groups, has revealed to have antiviral activity for a broad range of viruses in vitro (Tay et al., 2013, Wagstaff et al., 2012). Report by Caly et al., ivermectin, is an inhibitor of the SARS-CoV-2, with addition to Vero-hSLAM cells two hours after infection with SARS-CoV-2 able to effect ~ a 5000-fold reduction in viral RNA at 48 hours (Caly et al., 2020). Patrì and Fabbrocini hypothesized that hydroxychloroquine and ivermectin could act consequentially and synergistically; Hydroxychloroquine would act by inhibition of the entry of the virus into the host cell, while ivermectin could decrease viral replication if the virus could get in, supporting hydroxychloroquine antiviral effects (Patrì and Fabbrocini, 2020). The National Veterinarians` Union In Bulgaria firmly discourages self-medication with ivermectin, where in this country is only available for use in animals. In April letter to stakeholders, FDA has similarly shared its worries on this issue and explicitly recommended against any attempts for self-medication with ivermectin for COVID-19 (Momekov and Momekova, 2020).

**Lopinavir-ritonavir**
Lopinavir is always combined with ritonavir to reduce the dose of lopinavir and raise the plasma levels of lopinavir as ritonavir inhibits CYP3A isoenzyme. Lopinavir-ritonavir are antiretroviral protease inhibitors used as a second-line drug for the management of HIV-1 infection in adults and children and they have limited side effects profile (Bhatnagar et al., 2020). Protease is a key enzyme in coronavirus polyprotein processing and lopinavir/ritonavir has anti coronavirus activity in vitro (Şimşek Yavuz and Ünal, 2020). In a previous control study, lopinavir/ritonavir with ribavirin amongst SARS-CoV patients was related to substantial clinical benefit. The adverse clinical outcome was significantly lower in the treatment group than in the controls who treated only with ribavirin on day twenty-one after the beginning of symptoms (Chu et al., 2004). Recently the NEJM published an original article about the trial of Lopinavir–Ritonavir in 199 hospitalized adult patients with COVID-19, no benefit was detected with this treatment beyond standard care group. Mortality at 28 days was similar between these two groups (Cao et al., 2020a). clinical findings from a case report of the index patient who was the first to cause tertiary transmission outside China. After lopinavir/ritonavir was administered, β-coronavirus viral loads decreased significantly and little coronavirus titers were detected (Lim et al., 2020). As a result of the case series reported in Wuhan, China, after completion of the follow-up period no significant effect on survival

was observed in patients with ARDS (Liu et al., 2020b). In an open-label, controlled trial of eighty patients with COVID-19, thirty-five patients who received oral favipravir plus interferon by aerosol inhalation were compared with forty-five patients who received lopinavir/ritonavir plus by aerosol inhalation. The favipiravir group showed shorter viral clearance time. Also showed marked improvement in chest imaging compared with the control group (Cai et al., 2020).

**Oseltamivir, paramivir, zanamivir, ganciclovir and, acyclovir** Antiviral drugs commonly used in clinical practice, are ineffective for 2019-nCoV and not recommended (Mrs. Sheeliya et al., 2020).

**Remdesivir**

Remdesivir is a novel adenosine analog, which incorporates into nascent viral RNA chains and results in premature termination (Wang et al., 2020b). It is a prodrug that is intracellularly metabolized to an analog of adenosine triphosphate that could inhibit viral RNA polymerases(Cao et al., 2020c). Remdesivir has broadspectrum activity against several virus families, including filoviruses and coronaviruses, and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses (Grein et al., 2020). Recently reports showed that therapeutic RDV enhanced disease outcomes and decreases viral loads in SARS-CoV-infected mice (Sheahan et al., 2020, Sheahan et al., 2017). The first case to present with SARS-CoV-2 in the U.S. was treated on the seventh day of hospitalization, and his condition was reportedly improving on the eighth day with parenteral remdesivir in January 2020 (Amirian and Levy, 2020). Remdesivir was well tolerated, although transitory gastrointestinal upset and elevated aminotransferase levels were reported. Treatment discontinuation after respiratory symptoms improvement (total duration of four days, five days, and ten days) (Holshue et al., 2020). remdesivir showed proper safety and pharmacokinetics profile in phases I trials (Pedersen et al., 2019). Phase II clinical trials have revealed human tolerance to remdesivir. Of the 175 patients in phase II clinical trial administering remdesivir, nine were stated to have severe adverse reactions, eight of whom were considered not related to drugs(Mulangu et al., 2019). In China, there are two currently ongoing phases 3, randomized, double-blind, placebo-controlled multicentre clinical trials. They have been submitted to https://clinicaltrials.gov on 31 January 2020 and are designed to evaluate the efficacy and safety of parenteral remdesivir in hospitalized adults with mild-to-moderate and severe COVID-19, i.e., NCT04257656 (https://clinicaltrials.gov/ct2/show/NCT04257656) and NCT04252664 (https://clinicaltrials.gov/ct2/show/NCT04252664) (Ko et al., 2020).

**Ribavirin**

Ribavirin is a guanosine analog antiviral that interferes with the replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis, has antiviral activity against many distinct viruses in vitro and in vivo (Graci and Cameron, 2006). The low cost of ribavirin and wide availability support its potential to significantly impact the treatment of nCoV infections (Khalili et al., 2020). Whereas promising results were attained with ribavirin and interferon α2b in a MERS-CoV rhesus macaque model (Falzarano et al., 2013), data have been inconsistent on patients with MERS-CoV infections that were treated with a combination of ribavirin and interferon (either α2a or β1) (Arabi et al., 2017). On the other hand, ribavirin decreases hemoglobin concentrations. This feature diminishes its potential as an antiviral option against SARS-CoV-2 (Arabi et al., 2017). In the first published case series of 2019-nCoV treatment (total of 138 cases), no patients have been reportedly treated with ribavirin (Wang et al., 2020a). several ongoing controlled clinical trials evaluating ribavirin in combination with other treatments: Lopinavir/ritonavir, ribavirin, and IFN-β combination for nCoV treatment NCT04276688, and Ribavirin + IFN-α1b One arm in prospective, parallel design interventional trial ChiCTR2000029387.

**Tocilizumab**

Interleukin-6 (IL-6) is a cytokine that has a central role in the inflammatory and immune response (Kaur et al., 2020). Recent clinical experiences in China proposed that IL-6 is a key cytokine involved in COVID-19-induced cytokine storms. So, Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, is recommended in severely ill patients with elevated IL-6 by (Luo et al., 2020). A recently published case report of a 42-year-old male patient with a respiratory failure related to COVID-19 who had a quick favorable consequence after two infusions of tocilizumab. This recommends that anti-IL6 receptor inhibitor treatment might reduce the risk of progression to SARS by modifying the cytokine storm in the lungs with COVID-19 (Michot et al., 2020). In a single-center experience intended to discuss the treatment response of Tocilizumab therapy in COVID-19, Luo et al. enrolled fifteen critically ill patients with COVID-19. Tocilizumab treatment ameliorated the increased c-reactive protein in all patients rapidly and appears to be an effective management option in COVID-19 patients with at high risk of cytokine storms. (Luo et al., 2020). Another study evaluates the effectiveness of Tocilizumab for Severe COVID-19 Patients, it reported a remarkable improvement within a few days, the fever returned to normal. 15 of the 20 patients involved in the study had lowered their oxygen requirements and one patient stopped oxygen therapy. The lymphocytes percentage decreased in 85.0% patients in comparison to before treatment, returned to normal in 52.6% patients on the fifth day (Xu et al., 2020).

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