



A REVIEW ON POSSIBLE PHARMACOLOGICAL OPTIONS AGAINST COVID-19

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ABSTRACT

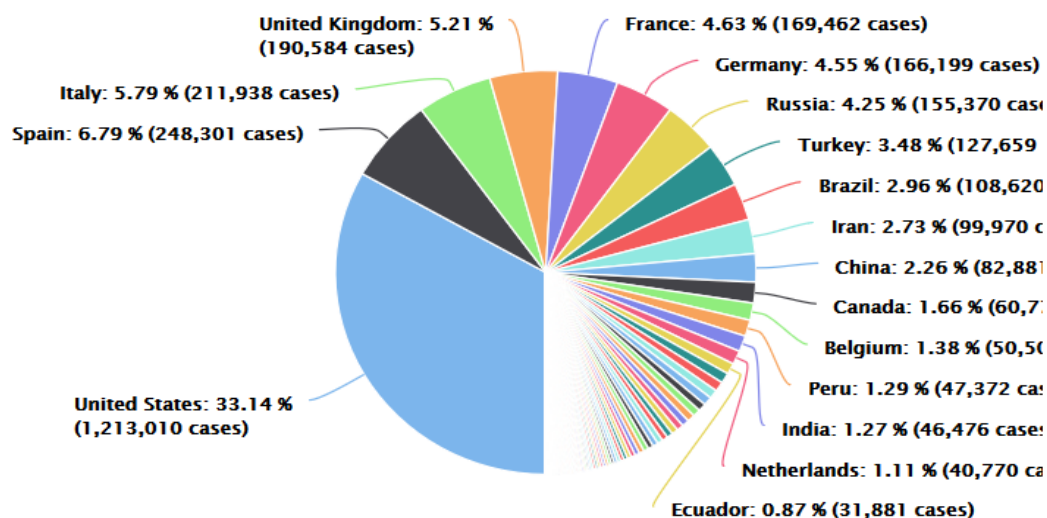
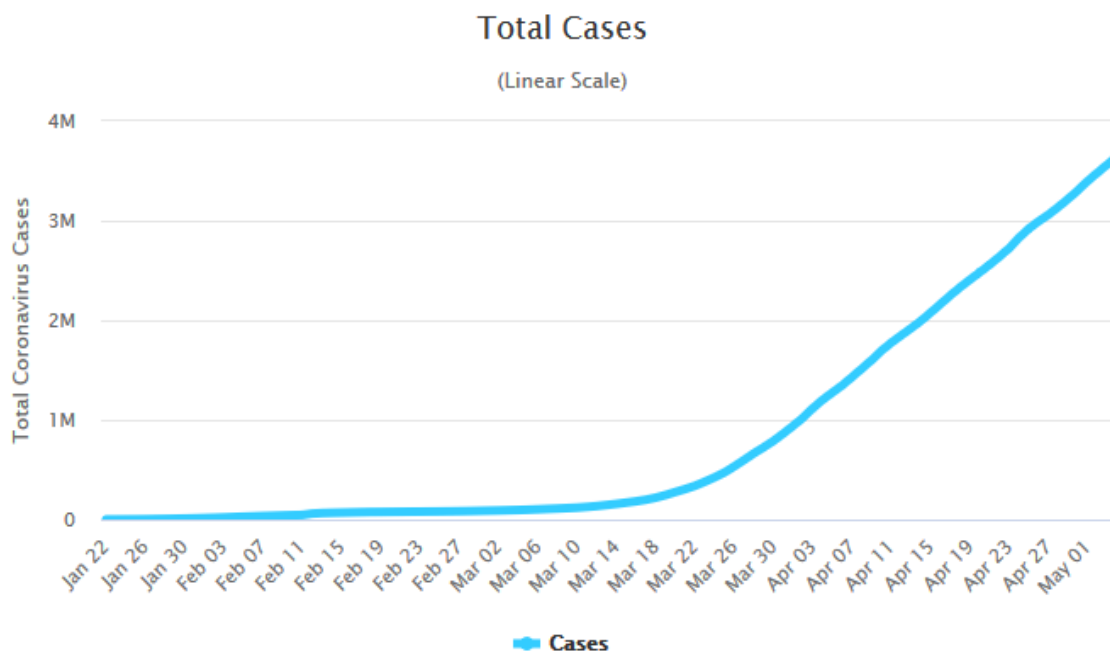
The spread of Severe acute respiratory syndrome 2 (SARS-Cov-2), the causative agent of coronavirus disease (COVID-19) has become a public health emergency. The whole world is concerned about the pandemic of COVID-19 caused by widespread SARS-CoV-2 across the globe. This new disease and its causative virus have drawn its major global attention. The number of patients and death rates are continuously increasing. The research community and scientists have been conducting a major campaign to understand this new emergent disease and its epidemiology to uncover possible treatment regimens, discover effective therapeutic agents, and develop vaccines. Since SARS-CoV-2 is a newly discovered pathogen, no specific drugs have been identified or are currently available. Although, a few candidates have shown efficacy in vitro studies, as well as in pre-clinical studies, and some drugs have also shown efficacy in clinical practice, but not a single drug has proven effective in large clinical randomized clinical trials. This review summarizes the ongoing advances and clinical trials designing the therapeutics against COVID-19. The whole is waiting for the results of these clinical trials as a potential treatment against COVID-19.

KEYWORDS: COVID-19, coronavirus, pharmacotherapy, treatment.

INTRODUCTION

The coronavirus disease (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2). The first case of COVID-19 reported in late December, 2019, and more patients reported with the same disease over the following days. Although, the epicenter of this disease was located in Wuhan, China.^[1] The disease spread rapidly outside of China to the whole world through human transmission by respiratory droplets, and eventually, the World Health Organization declared a pandemic on March 11, 2020.^[2] Now it has spread to more than 180 countries (figure 1) with over 3,442,234 confirmed cases (figure 2) and confirmed 239,740 deaths worldwide as of May 5, 2020.^[3]

Distribution of cases

Figure 1: photo taken from www.worldmeter.com on May 5, 2020.Figure 2: Photo taken from www.worldmeter.com on May 5, 2020.

The number of cases and the death rates are still increasing. It has been reported that the most severe cases and mortality are associated with comorbidities. The most common associated underlying health conditions are diabetes mellitus, pulmonary disease, and old age.^[4] Since SARS-Cov-2 is a newly discovered pathogen, there is no specific drug or vaccine available to date. The researchers and the scientific community have been racing to find the best possible treatment for COVID-19 to save the lives. The current situation demands urgent treatment against COVID-19. Many

treatment options have been proposed, and it has been thought that already existing drugs can be repurposed for use in the treatment of COVID-19. Several drugs like chloroquine, hydroxychloroquine, remdesivir, favipiravir, lopinavir, ritonavir, and tocilizumab, and many other drugs are under trials to determine the efficacy and safety against COVID-19 treatment. Although remdesivir and hydroxychloroquine have proven effective in clinical studies on a small scale, no single pharmacological therapy has shown efficacy in large randomized clinical trials.^[5,6] In this review, we

have summarized available data on remdesivir, chloroquine, lopinavir/ritonavir, and tocilizumab for the use against COVID-19 and undergoing clinical trials on these drug against COVID-19.

Remdesivir

Remdesivir is an analog of adenosine nucleotide developed by Gilead Sciences for the Ebola virus, which is converted to its active metabolite GS-5734 that binds to RNA dependent RNA polymerase and inhibits the viral synthesis by chain termination. Remdesivir has proven effective against the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV in both in-vitro studies and animal models especially in the rhesus monkey.^[7,8] Remdesivir also has shown antiviral activity against SARS-CoV-2 in vitro studies.^[9] The efficacy and safety of remdesivir has also been reported in clinical studies and in the early results of clinical

trials.^[5,10] The first case of COVID-19 in the USA treated with compassionate remdesivir on hospital day seven due to persistent fever and developing chest infection. His symptoms improved and oropharyngeal swab on hospital day eight was negative, but nasopharyngeal swab was positive. Patient has been reported well with no adverse events.^[10] Three patients were treated with compassionate use of remdesivir among the 12 patients confirmed by the Center for Disease Control (CDC). All the patients have reported recovered with few side effects like gastrointestinal symptoms and liver enzymes elevations. WHO has also given the emergency approval of remdesivir against COVID-19, but it has not proven effective in large-sized clinical trials. Ongoing trials on remdesivir available at <https://clinicaltrials.gov/> are given in table 1. The results of these trials are expected soon.

Table 1: Trials on remdesivir.

Clinical trial ID	Status	Study Results	Conditions	Interventions	Locations
NCT04302766	Available	No Results Available	COVID-19	Remdesivir	USA
NCT04280705	Recruiting	No Results Available	COVID-19	Placebo and Remdesivir	USA
NCT04315948	Recruiting	No Results Available	COVID-19	Remdesivir and other standard care	France
NCT04315948	Recruiting	No Results Available	COVID-19	•Drug: Remdesivir • Other: Standard of care	France
NCT04314817	Recruiting	No Results Available	COVID-19	•Drug: Any drug used to treat Covid-19	France
NCT04292899	Recruiting	No Results Available	COVID-19	•Drug: Remdesivir •Drug: Standard of Care	USA
NCT04292730	Recruiting	No Results Available	COVID-19	•Drug: Remdesivir •Drug: Standard of Care	USA
NCT04321616	Recruiting	No Results Available	COVID-19	•Drug: Remdesivir •Other: (Standard of Care) SoC	Norway

Chloroquine/hydroxychloroquine

Chloroquine is an antiprotozoal drug used to treat malaria, and hydroxychloroquine is an analog of chloroquine used in the treatment of common medical conditions, especially in rheumatoid arthritis and prophylaxis for malaria. Chloroquine has also been considered as a potential drug against COVID-19 because it inhibited the viral activity in vitro study.^[9] Chloroquine acts via elevating the endosomal pH and interferes with ACE2 glycosylation. Hydroxychloroquine has also shown efficacy against SARS-CoV-2 in vitro study.^[11] In a recent study, it has been reported that 200 mg of oral hydroxychloroquine every 8 hours is sufficient for viral inhibition and eradication. The eighteen patients who received hydroxychloroquine out of 36 patients showed better results in terms of efficacy and safety as compared to the standard care regimen. It was also observed that the addition of azithromycin to hydroxychloroquine resulted in far superior results in azithromycin subgroups vs in those patients who received only hydroxychloroquine. Although efficacy of chloroquine/hydroxychloroquine has been observed in clinical practice, it has not proven effective in large clinical trials yet, and the results of these trials are awaited. The clinical trials on chloroquine and hydroxychloroquine are given in table 2.

Table 2: Trials on chloroquine/hydroxychloroquine.

Clinical trial ID	Status	Study Results	Conditions	Interventions	Locations
NCT04316377	Recruiting	No Results available	COVID-19	•Drug: Hydroxychloroquine Sulfate	Norway
NCT04341727	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine Sulfate •Drug: Azithromycin •Drug: Chloroquine Sulfate	United States
NCT04346667	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine Sulfate Regular dose. Drug: Hydroxychloroquine Sulfate Loading Dose. Drug: Chloroquine	Pakistan
NCT04322396	Recruiting	No Results Available	COVID-19	•Drug: Azithromycin •Drug: Hydroxychloroquine	Denmark
NCT04351191	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine Sulfate Regular dose. Drug: Hydroxychloroquine Sulfate Loading Dose	Pakistan
NCT04325893	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine •Drug: Placebo	France
NCT04353037	Recruiting	No Results Available	COVID-19	•Drug: Group A HCQ •Drug: Group B Control	United States
NCT04324463	Recruiting	No Results Available	COVID-19	•Drug: Azithromycin •Drug: Hydroxychloroquine or Chloroquine	Canada
NCT04321278	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine + azithromycin •Drug: Hydroxychloroquine	Brazil
NCT04344951	Recruiting	No Results Available	COVID-19	•Drug:(Chloroquine phosphate) 200mg tablets	Greece
NCT04323345	Recruiting	No Results Available	COVID-19	•Dietary Supplement: Natural Honey •Other: Standard Care	Egypt
NCT04342221	Recruiting	No Results Available	COVID-19	•Drug: Hydroxychloroquine Sulfate •Drug: Placebo	Germany
NCT04351724	Recruiting	No Results Available	COVID-19	•Drug: Chloroquine or Hydroxychloroquine •Drug: Lopinavir/Ritonavir	Austria

Favipiravir

Favipiravir is ribonucleic acid (RNA) dependent RNA polymerase inhibitor developed against Ebola virus. Favipiravir has broad-spectrum antiviral activity, and it acts as an alternate substrate in viral replication, which results in inhibition of viral replication. Favipiravir has also demonstrated efficacy against SARS-CoV-2 in vitro

study. A high EC₅₀ (decreased potency) against SARS-CoV-2 has been observed in protecting mice against Ebola virus despite similarly high EC₅₀ values.^[12] Favipiravir is also under trials to determine the efficacy against COVID-19. Favipiravir has not proven effective, and the results of these trials (table 3) are underway.

Table 3: Clinical trials on favipiravir.

Clinical trial ID	Status	Study Results	Conditions	Interventions	Locations
NCT04319900	Recruiting	No Results Available	COVID-19	•Drug: favipiravir tablets+chloroquine phosphatetables tablets •Drug: Favipiravir tablets •Drug: Placebo	China
NCT04310228	Recruiting	No Results Available	COVID-19	•Drug: Favipiravir Combined With Tocilizumab •Drug: Favipiravir •Drug: Tocilizumab	China
NCT04333589	Recruiting	No Results Available	COVID-19	•Drug: Favipiravir	China
NCT04356495	Not yet recruiting	No Results Available	COVID-19	•Drug: Imatinib •Drug: Favipiravir	France
NCT04359615	Not yet recruiting	No Results Available	COVID-19	•Drug: Favipiravir •Drug: Hydroxychloroquine	Iran

Lopinavir/ritonavir

Lopinavir is an anti-HIV drug. It belongs to the class of protease inhibitors. It is used in combination with ritonavir against HIV. Lopinavir inhibits viral proteases involved in the replication of the virus. Ritonavir is a potent inhibitor of CYP3A4 and thus increases the concentration of lopinavir and enhances the antiviral activity of lopinavir. Lopinavir has inhibited viral replication by blocking the proteases of the SARS-CoV-1 in-vitro study.^[13] Lopinavir, in combination with ribavirin, has shown efficacy against SARS-CoV-1 in an animal model. Lopinavir/ribavirin inhibited the viral replication after forty-eight hours of the incubation period.^[14] The effective concentration (EC_{50}) of 17.1 ± 1 was observed in Vero cells against SARS-CoV-1.^[15] Young et al. reported that five out of 18 patients

diagnosed with COVID-19 were treated with lopinavir in combination ritonavir. Three patients showed a marked reduction in oxygen requirement after being started on lopinavir/ritonavir. A decrease in viral load and improvement in physical health was also observed in 2 patients.^[16] Lopinavir, in combination with ritonavir, did not show any significant activity against COVID-19 in the published result of a randomized clinical trial, in terms of primary endpoints, mortality, time to discharge from hospital, and the virologic response on repeat oropharyngeal swab throughout the study.^[17] With the available data and information, it is difficult to assess the efficacy and safety of lopinavir as monotherapy or in combination with ritonavir. Clinical trials on lopinavir/ritonavir are given in table 4. The results of these clinical trials are not available yet.

Table 4: Clinical trials on lopinavir and ritonavir.

Clinical trial ID	Status	Study Results	Conditions	Interventions	Locations
NCT04252885	Recruiting	No Results Available	COVID-19	•Drug: Lopinavir and Ritonavir Tablets •Drug: Arbidol	China
NCT04307693	Recruiting	No Results Available	COVID-19	•Drug: Lopinavir/ritonavir •Drug: Hydroxychloroquine sulfate	South Korea
NCT02845843	Recruiting	No Results Available	COVID-19	•Drug: Combination of Lopinavir /Ritonavir and Interferon beta-1b •Drug: Placebo	Saudi Arabia
NCT04276688	Completed	No Results Available	COVID-19	•Drug: Lopinavir/ritonavir •Drug: Ribavirin •Drug: Interferon Beta-1B	Hong Kong
NCT04321174	Recruiting	No Results Available	COVID-19	•Drug: Lopinavir/ritonavir	Canada
NCT04251871	Recruiting	No Results Available	COVID-19	•Drug: inhalation, and lopinavir/ritonavir)	China
NCT04315948	Recruiting	No Results Available	COVID-19	•Drug: Remdesivir •Drug: Lopinavir/ritonavir •Drug: Hydroxychloroquine	France
NCT04351724	Recruiting	No Results Available	COVID-19	•Drug: Chloroquine or Hydroxychloroquine •Drug: Lopinavir/Ritonavir	Austria
NCT04314817	Recruiting	No Results Available	COVID-19	•Drug: Any drug used to treat Covid-19	France
NCT04323345	Recruiting	No Results Available	COVID-19	•Dietary Supplement: Natural Honey •Other: Standard Care	Egypt
NCT04328012	Recruiting	No Results Available	COVID-19	•Drug: lopinavir/ritonavir •Drug: Hydroxychloroquine Sulfate •Drug: Placebos	United States
NCT04343768	Completed	No Results Available	COVID-19	•Drug: Hydroxychloroquine •Drug: Lopinavir / Ritonavir	Iran

Tocilizumab

Tocilizumab belongs to class of humanized monoclonal antibody which has its activity against membrane-bound and soluble interleukin-6 (IL-6) receptors which are secreted by immune cells of the body in response to inflammation. Tocilizumab is widely used against rheumatoid arthritis as well as used as chimeric antigen receptor T-cell (CAR T) therapy for the treatment of patients with cytokine release syndrome.^[18] It has been reported that a surge of IL-6 has been observed in severe cases of COVID-19 as well as in those patients who

could not survive.^[19] Twenty-one patients treated with tocilizumab showed a marked reduction in the severity of disease. Reduction in the use of oxygen therapy, fever, and C- reactive protein was also observed.^[20] More data is required regarding the use of tocilizumab against COVID-19, and randomized clinical trials are underway to determine the efficacy of tocilizumab (table 5).

Table 5: Clinical trials on tocilizumab.

Clinical trial ID	Status	Study Results	Conditions	Interventions	Locations
NCT04335071	Recruiting	No Results Available	COVID-19	•Drug: Tocilizumab (TCZ) •Drug: Placebo	Switzerland
NCT04310228	Recruiting	No Results Available	COVID-19	•Drug: Favipiravir Combined With Tocilizumab	China
NCT04322773	Recruiting	No Results Available	COVID-19	•Drug: RoActemra iv •Drug: RoActemra sc •Drug: Kevzara sc	Denmark
NCT04359667	Recruiting	No Results Available	COVID-19	•Drug: Tocilizumab 20 MG/ML Intravenous Solution [ACTEMRA]	Croatia
NCT04339712	Recruiting	No Results Available	COVID-19	•Drug: Anakinra •Drug: Tocilizumab	Greece
NCT04335305	Recruiting	No Results Available	COVID-19	•Drug: Tocilizumab •Biological: Pembrolizumab (MK-3475)	Spain
NCT04361552	Recruiting	No Results Available	COVID-19	•Other: Best Practice •Biological: Tocilizumab	United States
NCT04330638	Recruiting	No Results Available	COVID-19	•Drug: Anakinra •Drug: Siltuximab •Drug: Tocilizumab	Belgium

Many other drugs like arbidol, corticosteroids, ribavirin, oseltamivir, baloxavir, and bevacizumab, etc. are under clinical trials justifying that the scientific community is working hard to come up with the current situation. These trials are different in study nature, study structure, and population size. These trials are also different in the severity of disease and dosing regimen. The results of these trials are not available yet. WHO has given the emergency approval of remdesivir and chloroquine against coronavirus. The use of these medicines should be based on the patient's clinical status and the severity of the disease.

Conclusion and perspective

The proper evaluation and appropriate management techniques against COVID-19 are rapidly evolving. The best possible regimen to treat the infection or to prevent the disease progression to critical is still challenging. Many drugs listed in this article are encouraging, and even some candidates have shown efficacy in clinical practice. However, the potential benefit of the therapy on a large-sized population is yet to determine. There should be a well-defined strategy for those patients who warrant therapy. The timing of initiation of therapy and dosing of therapy is also considered important. The rapid initiation of therapy should be considered in all those patients who are hospitalized either in the context of WHO guidelines or randomized controlled clinical trials. The researchers are struggling hard for an effective and potential candidate to control the COVID-19 effectively. As there is no potent medicine available to date against COVID-19, we have to rely on measures, especially strict preventive and control measures, which might help in minimizing the risk of disease spread. The current situation demands urgent treatment for COVID-19. Safety and efficacy related data from the highly randomized controlled clinical trials are needed.

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