Comprehensive Literature Review and Evidence evaluation of Experimental Treatment in COVID 19 Contagion

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ABSTRACT

IMPORTANCE: Coronavirus 2019 pandemic (COVID 19) is caused by the Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus. The pandemic is affecting the livelihood of millions of people all over the world. At the time of preparing this report, the pandemic has affected 1 827 284 patients, with 113 031 deaths in 185 countries as per Johns Hopkins University. With no proven treatment for the disease, prevention of the disease in the community and healthcare setting is need of the hour.

OBJECTIVE: To perform a comprehensive literature search for preventive measures and experimental treatment options. In this review, we have focused our discussion on the risk of disease transmission, supportive treatment, and possible treatment options based on available evidence.

EVIDENCE REVIEW: We performed a literature search on google scholar, PubMed, and society guidelines for literature related to COVID 19 and previous coronavirus pandemics. We included data review articles, observational studies, and controlled trials to synthesize the treatment options for COVID 19.

FINDINGS: In this article, we have extensively reviewed and discussed recommendations from various world organizations for the public and healthcare workers. We have also discussed currently available experimental treatments since there is no proven treatment for COVID 19. The best method of dealing with the current outbreak is to reduce the community spread and thus "flatten the curve." Although Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, and Azithromycin have been tried, passive immunity through convalescent serum and vaccine is still at an experimental stage. Patients with severe COVID 19 infections could be considered for this experimental treatment through various national randomized control trials, which may eventually lead to an evidence-based treatment strategy.

CONCLUSIONS AND RELEVANCE: Awareness of currently available experimental treatment among healthcare providers and exploration of possible treatment options through evidence is need of the hour. We have discussed the most recently available literature and evidence behind experimental treatment in this article.

KEYWORDS: COVID-19, coronavirus, Wuhan, Remdesivir, pandemic, RT-PCR

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Background

The current coronavirus pandemic (COVID 19) is caused by Severe acute respiratory syndrome coronavirus 2 (SARS CoV 2), a positive-sense single-stranded RNA virus. The initial disease outbreak started in China as a cluster of pneumonia due to unclear etiology. The disease was linked to contact with the seafood and wet animal market in Wuhan city of Hubei province of China.[1] Eventually, the virus was identified as a novel coronavirus and named as SARS-CoV-2 by the World Health Organization (WHO).[2] The virus spread exponentially over the next few weeks to several countries, and WHO declared it as a pandemic on 11 March 2020. Since then, more than 1 827 284 patients have been diagnosed with a confirmed infection in 185 countries, with 113 031 deaths as per Johns Hopkins University.

The virus causes animal and human diseases affecting respiratory and gastrointestinal systems. The disease can be transmitted to when humans come in contact with secretions and body fluids of infected animals either through droplets or consumption of infected meat. Once the virus comes in contact with human respiratory and gastrointestinal mucosa, it uses entry receptors angiotensin-converting enzyme 2 (ACE2) to enter the human cells[3,4]. Transmission of disease between humans happens through secretions, droplets, and fecal-oral

contamination. The virus has been detected in sputum, nasopharyngeal secretions, respiratory droplets, blood, stool, and urine samples[5]. At this time, there is no evidence to suggest vertical transmission to the fetus during pregnancy. Experience in treating pregnant women with COVID 19 lacks to make a clear determination at this time[6]. The estimated incubation period for the SARS-CoV-2 virus is around 14 days, with a median of 4-5 days[7]. Common symptoms of COVID-19 include fever, cough, shortness of breath reported in more than 70% of patients. Other symptoms include headache, and myalgia. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, dysgeusia, anosmia, and liver involvement have also been observed[7,8,9].

Preventive measures

Precautions for prevention of SARS-CoV-2 transmission is the avoidance of contact with infected patients. The Center for Disease Control (CDC) has made several recommendations to the general population, including; hand hygiene, avoiding contact, and clean and disinfect.

Hand hygiene: Washing hands with soap and water for at least 20 seconds or using alcohol-based hand sanitizers with at least 60% alcohol content covering all the areas can kill the virus.

Avoiding close contact: The most common mode of transmission between humans is through respiratory droplets. Maintaining at least 6 feet distance from anybody suspected of infection reduces the chance of droplet infection. However, there have been documented cases of COVID transmission from asymptomatic carriers without any disease manifestations. Those who are sick should stay home and seek medical help if symptoms are worsening or deteriorating. If someone is sick, they should wear a mask to reduce the risk of transmission to others.[10] The most important and widespread intervention to prevent the rapid increase in cases is through social distancing. Center for disease control recommends at least 6 feet distance between individuals to prevent community spread of COVID 19. Various state governments, including New York and California, have implemented statewide stay home, and more states are following similar social distancing.[11] The main aim of the goals is to flatten the epidemiological curve and reduce the total number of sick patients at a given time. This strategy will help hospitals to use their resources in a manner without compromising care for anybody. However, with the rising death toll in Italy and elsewhere in the world, the rise in the number of sicker patients requiring inpatient hospital care is expected.

Clean and disinfect

It is already established that the COVID virus can survive on a variety of objects, fomites, and surfaces, including plastic, steel, and medical instruments, for up to 72 hours at infectious titers.[12] Although there is no documented case of COVID 19 transmission from the surface to humans, the possibility is real. CDC recommends using bleach 5 tablespoon bleach in 1 gallon of water or alcohol-based disinfectant with at least 70% alcohol.

Prevention of COVID 19 transmission in healthcare institutions

The transmission of COVID 19 in the health care setting can prove deadly. Since health care workers starting from receptionists, nurses, phlebotomists, and treating physicians all are at risk of contracting COVID 19 through various body fluids and respiratory droplets, it is paramount to practice all safety precautions. All patients with suspected or confirmed COVID 19 infection should be isolated with contact, airborne, and droplet precautions with negative pressure ventilation rooms. Whenever the patient needs to be transferred to the procedure room or operative theaters, patients should wear a surgical mask.

The most important rule in caring for COVID 19 patients is to minimize the number of healthcare workers exposed. Any non-essential members such as residents, fellows who are not making critical decisions should be assigned for other tasks such as answering COVID 19 helplines and telemedicine virtual visits.

Any healthcare workers who come in contact with suspected on confirmed COVID 19 patients should follow the following basic personal protection measures before entering the room:

a. Gloves
b. Disposable waterproof gown
c. Face shield or Eyeshields/goggles
d. N95 or other high filters respirators (FFP2 and FFP3)
e. Hand wash with soap and water or disinfectant hands with alcohol-based sanitizers that have at least 60% alcohol before and after entering the room

Cleaners who clean the rooms that are occupied by the COVID 19 patients should also follow the above precautionary measures. They should remove the glove, and dispose of them according to biohazards management per institutional policy after cleaning.[13,14]

Supportive treatment

Most patients with COVID 19 (80%) will recover from infection with minor symptoms of upper respiratory tract infection such as fever, cough, sputum production, and myalgia.[15] However, it is not clear what percentage of the infected patients will require hospitalization and what percentage of hospitalized patients would end up requiring intensive care unit stay.

In 1 study involving 204 confirmed COVID patients, 7.8% of the patients required intensive care unit stay, and 17.6% of the patients died despite treatment.[16] As per available evidence, an overall case fatality rate of 2.3% to 3.6% has been observed.[5,17] However, the case fatality rate (CFR) is significantly higher for

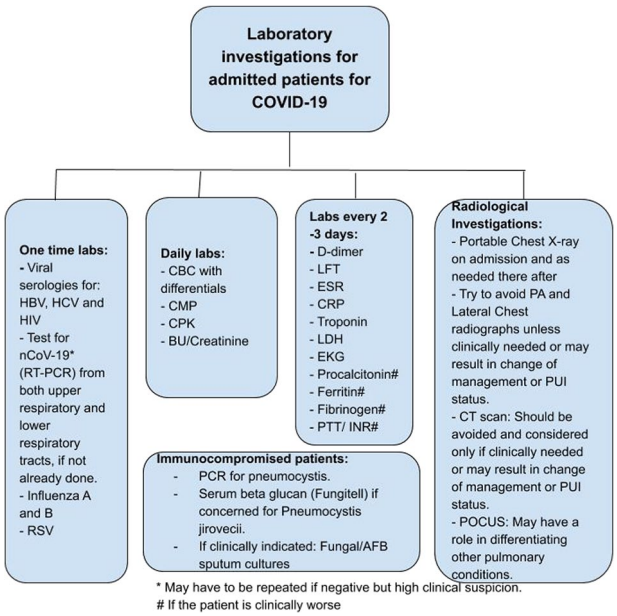

Figure 1. Treatment algorithm for COVID 19 treatment.

elderly patients and those with comorbidities and immunosuppression as high as 14.8%. In the same study, the CFR for patients that were diagnosed as critical had mortality of 49%.[18] Figure 1 shows an algorithm for the treatment of COVID 19 during inpatient care.

While symptomatic treatment with NSAIDs, treatment of secondary bacterial infections with antibiotics is the mainstay of treatment for COVID 19 patients, sicker patients may need respiratory support ranging from nasal cannula oxygen to ventilator support. Hospitals, medical, and surgical societies are recommending to reschedule any non-urgent procedures to mobilize resources for critically ill patients.[14]

Severe COVID 19 is defined as those who have at least 1 of the following symptoms including shortness of breath, respiratory frequency $\geqslant$ 30/minutes, oxygen saturation in the blood $\leqslant$ 93%, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio $<$ 300, or lung infiltrates $>$ 50% within 24 to 48 hours. The life-threatening disease is defined as 1 or more of these symptoms: respiratory failure, or septic shock, or multiple organ dysfunction or failure.[19]

Respiratory support

Patients with severe disease usually develop pulmonary symptoms due to acute respiratory distress syndrome, and the most common cause of death is hypoxemia. Therefore, respiratory support with a ventilator can reduce mortality drastically. However, if there is a massive rise in the number of cases and the need for ventilatory support is going to be significantly high. Hospitals do not have the capacity to manage such a high number of patients with critical care needs. There are not enough critical care providers or other resources such as ventilators, respiratory therapists, and critical care trained nurses. This can increase the mortality during COVID 19 outbreak. One of the most important aspects of caring for ARDS is low pressure and low volume lung-protective strategy. Guidelines suggest low tidal volume ($<$6 ml/kg), plateau pressure ($<$30 m Hg), arterial pH $<$7.30, Oxygenation (PaO2 $>$ 55, SpO2 between 88% and 95%. And weaning off of the ventilator should be attempted when Fio2/PEEP $<$ 0.40/8.[20]

With a possibility of ventilator shortage during the COVID 19 pandemic, it is important to utilize personnel and equipment such as ventilators efficiently. In an experimental pilot study, a single ventilator was connected to 4 lung simulator bags representing 4 different patients. Although the study found that it was theoretically possible to manage 4 patients on a single ventilator, there were several limitations.[21]

Anti-hypertensive medications and anti-inflammatory medications

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the symptomatic treatment for the treatment of most viral illnesses. A recent correspondence letter published in a major medical journal suggested that the use of Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) among patients with hypertension and diabetes may have upregulated ACE2 receptors. Similarly, ibuprofen and thiazolidinediones also cause the upregulation of ACE2 receptors. Since SARS-CoV-2 uses ACE2 receptors to enter the host cell, it was hypothesized that these patients might develop severe and COVID 19.[22] However, there is no proven benefit or adverse effect of NSAIDs or ARBs observed in the treatment of COVID 19. Future research on the topic may be necessary before we can make any further determinations.

Corticosteroids are the other potent anti-inflammatory medication that has been used in the treatment of COVID. However, there is no clinically proven benefit or harm in using corticosteroids in the treatment, and therefore, further studies are needed to evaluate corticosteroids for the treatment of COVID.

Review of experimental treatments

Currently, there is no clinically proven medication available for the treatment of COVID 19 patients. Various agents such as Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, and Azithromycin are being evaluated. Other experimental medications include interleukin 6 antibodies (tocilizumab).[23] Table 1 lists the medications, dosage, administration, and monitoring required while treating COIVD 19 patients.

Antimalarial drugs: Chloroquine and hydroxychloroquine

Antimalarial drug chloroquine has shown in vitro activity against multiple viruses, including Enterovirus EVA71, zika

Table 1. Medications available and important information.

DRUGS	DOSAGE	MECHANISM	ADMINISTRATION	DRUG MONITORING
Hydroxychloroquine (Plaquenil®). NOT FOR USE AS PROPHYLAXIS	400 mg (2 × 200 mg tablets) PO q12h × 2 doses on day 1, then 200 mg PO q12h on days 2-5	Alter pH at the surface of the cell membrane and inhibit nucleic acid amplification	Administer tablets with a meal. If needed, crush and allow at least 5 min to disperse the tablet in water.	Adverse events: retinal pathology, cardiac effects including cardiomyopathy and QTc prolongation, worsening of psoriasis/ porphyria, myopathy, neuropathy, neuropsychiatric events, hypoglycemia Contraindications: QTc > 500 msec drug interaction; Myasthenia gravis Porphyria Retinal pathology Epilepsy
Azithromycin	500 mg day 1, then 250 mg day 2-5	Synergy with hydroxychloroquine	Can be administered IV or PO given in combination with Hydroxychloroquine	*MONITOR CLOSELY FOR QTC PROLONGATION AS BOTH AZITHROMYCIN AND HYDROXYCHLOROQUINE MA
Lopinavir/ritonavir (Kaletra®)	400/100 mg (2 × 200/50 mg tablets) PO BID for up to 14 d	Inhibition of viral protease	Administer tablets with or without meals. Not crushable	Adverse events: GI intolerance, pancreatitis, asthenia, hyperlipidemia, transaminase elevation, hyperglycemia, insulin resistance/ diabetes mellitus, fat maldistribution, possible increase in the frequency of bleeding episodes in patients with hemophilia, EKG changes. Please obtain an HIV test prior to initiation and check for drug-drug interactions
Darunavir/ritonavir (Prezista®/Norvir®)	800/100 mg PO daily (ordered as 1 tablet of each agent daily)	Inhibition of viral protease	THE TWO TABLETS MUST BE GIVEN AT THE SAME TIME. Administer tablets with a meal. Not crushable	Adverse events: skin rash, hepatotoxicity, GI intolerance, headache, hyperlipidemia, serum transaminase elevation, hyperglycemia, fat maldistribution, possible nephrotoxicity with cobicistat Please obtain an HIV test prior to initiation and check for drug-drug interactions

virus, influenza A H5N1, and human coronaviruses.[24-27] Currently, efforts are being made to evaluate hydroxychloroquine in the treatment of SARS-CoV-2 infection. However, a similar hypothesis tested in a randomized double-blinded placebo-controlled trial for the treatment of H5N1 influenza during the outbreak in 2011 did not prevent infection.[28] Similarly, the treatment of Ebola infection with chloroquine also failed to show benefits.[29]

Chloroquine and hydroxychloroquine can prevent the cellular entry of the SARS-CoV-2 virus and thus preventing viral replication and, thus, the disease. SARS-CoV-2 utilizes spike (S) protein to bind to ACE2 receptors for cell entry. Chloroquine and hydroxychloroquine reduce the endosomal pH, prevent virus-cell fusion, and interfere with glycosylation of ACE2 receptors. This prevents spike protein from binding to entry (ACE2) receptors and thus preventing the viral replication.[30-32]

Initial experience to treat COVID 19 with chloroquine from Chinese hospitals has shown to reduce the severity of pneumonia, viral clearance, duration of symptoms with minimal side effects.[33] In another nonrandomized control study combination of hydroxychloroquine and azithromycin led to virologic cure at day 6 in 100% of the patients, whereas only 70% of the patients with hydroxychloroquine as monotherapy and 12.5% in the controlled group.[34] Larger randomized control trials are needed to establish the benefit of chloroquine and hydroxychloroquine in the treatment of COVID 19. In a recent update, the United States Food and Drug Administration has cautioned about the use of either Chloroquine or hydroxychloroquine since they have not shown to be safe and beneficial based on preliminary results, as well as concern regarding cardiotoxicity.[35] Therefore, their use has been restricted to clinical trials only.

Antiviral agents

Normal interferon response is a critical defense against viral infection and replication in the host cells. Beta coronaviruses such as Severe acute respiratory syndrome (SARS) virus, Middle Eastern Respiratory Syndrome (MERS), and SARS-CoV-2 (COVID19) viruses induce downregulation of interferon response which is critical to their pathogenicity.[36] Several antiviral agents have been proposed for the treatment of COVID.

1) **Remdesivir:** Remdesivir is a broad-spectrum antiviral agent with activity against several viruses, including paramyxoviruses, filoviruses, and human coronaviruses such as MERS and SARS. Remdesivir is an adenosine nucleotide analog shown to prevent MERS infection when given prophylactically and reduce the viral load, pulmonary symptoms when given in early disease in animal studies.[37,38]
In an in vitro study effect of medications targeting RNA dependent RNA polymerase (RdRp) of SARS CoV-2 was tested. And among them, Remdesivir, Galidesivir, Ribavirin, Sofosbuvir, ant Tenofovir were able to bind to the RdRp with sufficient binding energy, and this can

interfere in the replication of SARS CoV-2. Other agents with anti-RdRp agents under consideration are Setrobuvir, IDX-184 (a guanosine derivative), and YAK.[39] Lopinavir was also able to inhibit viral replication in another in vitro study; however, Ribavarin failed to inhibit virus replication in this study.[40]

In a recent cohort prospective study involving 53 patients with confirmed COVID 19 requiring supplemental O2, a ten-day course of Remdesivir was administered. At the end of 18 days follow up, and improved oxygen support class was observed. Among patients requiring mechanical ventilation, 57% (17 of 30) were extubated, and 47% (25 of 52) patients were discharged home. Mortality of 13% (7/52) was noted, of which mortality was 18% among those requiring invasive ventilation (mechanical ventilation or extracorporeal membrane oxygenation).[41] Further larger randomized, double-blinded, placebo-controlled trials are underway and would provide further information necessary to evaluate its efficiency in the near future.

2) **Lopinavir/Ritonavir**: Lopinavir is a protease inhibitor against HIV 1 when combined with ritonavir has shown activity against the SARS virus both in vitro and humans. Ritonavir is given in this combination to improve the plasma concentration of lopinavir. In a randomized control trial, a triple-drug regimen with Lopinavir/ritonavir and interferon-beta is being studied for MERS.[42] In another human transgenic mouse study, prophylactic and therapeutic properties of Remdesivir are being compared to Lopinavir/ritonavir and interferon-beta combination for the treatment of MERS.[43]

In a randomized control trial conducted in Wuhan province of China, Lopinavir/ritonavir was compared to standard treatment. The study showed no significant improvement in clinical improvement with lopinavir/ritonavir (Hazard ratio 1.24, 95% confidence interval [CI], 0.90 to 1.72). Also, there was no significant difference in mortality between the treatment group and the control group (12% vs 17%, 95% CI –17.3 to 5.7). Since this study was open-labeled, there is a high risk of bias.[44] Therefore, true double-blinded randomized control trials are needed to understand their benefit in the treatment of COVID 19.

Immunomodulators

Patients with acute respiratory distress syndrome (ARDS) in COVID 19 were noted to have cytokine storm of interleukin 6 (IL 6), interleukin 2, interleukin 7, interleukin 10, tumor necrosis factor α (TNF α), granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10) and many other cytokines.[45,46] Among these cytokines, IL 6 and G-CSF are the most important that lead to inflammation causing disruption of alveolar blood gas exchange, impaired oxygenation, and organ failure.

1) Corticosteroids. During the initial phase of the COVID-19 pandemic, the use of corticosteroids was in the treatment of severe COVID-19 was controversial. Immunosuppression due to corticosteroids could lead to increased susceptibility for secondary infection and worsen the outcome. However, the latest results show that corticosteroids may be beneficial. In a randomized control trial involving 6,425 patients, dexamethasone was administered to 2,104 patients, and 4,321 patients received usual care. The study showed that the 28-day mortality was significantly lower in the dexamethasone group (0.83; 95% Confidence Interval (CI) 0.75-0.93; p<001) when compared to usual care. The beneficial effects were mostly seen in those who had severe COVID-19 and not among those who were not receiving respiratory support.[47] Similarly, a meta-analysis of preliminary results from seven randomized control trials, corticosteroids significantly reduced the all-cause mortality (Pooled odds ratio 0.64 (95% CI, 0.50-0.82; $P < .001$).[48]

Current recommendations from the National Institute of Health suggests the use of dexamethasone 6mg per day for up to 10 days. If dexamethasone is not available, alternative corticosteroids such as prednisone, methylprednisolone, and hydrocortisone can be considered. However, the guidelines suggest against the use of corticosteroids for those who do not require supplemental oxygen.[49]

2) Tocilizumab: Interleukin 6 receptor monoclonal antibody. Tocilizumab is an interleukin 6 receptor monoclonal antibody used in the treatment of rheumatoid arthritis.[50] Tocilizumab binds to the IL 6 receptors and blocks the transmembrane signal transduction pathway that is responsible for the pro-inflammatory role of IL 6.

In a retrospective study, 21 patients with severe COVID 19 were treated with tocilizumab. Eighteen patients received just 1 dose, and 3 patients received a second dose. The study observed significant improvement in symptoms, improved oxygenation and reduced O2 demand (75%), a significant improvement in lymphocyte count (89.5%), improved lung infiltrates in 90% of the patients and 19 patients were discharged with no mortality at the time when the mean duration of hospitalization 13.5 ± 3.1 days.[51] It is a retrospective observational cohort study involving a small number of patients, and its results may not be generalizable. However, COVID 19 has no proven treatment, and a larger randomized, double-blinded controlled study is needed to further evaluate its efficacy. A recent meta-analysis has shown that the addition of Tocilizumab to the standard of care may reduce mortality.[52] However, the results were limited by the inclusion of observational studies only.

3) TNF α inhibitors. As previously described, ACE2 receptors play an important role in viral entry into the human cells and are responsible for lung injury.[3] It is observed that spike protein from the SARS CoV-2 virus causes TNF α converting enzyme-dependent shedding of ACE2 ectodomain.[53] This is critical in

viral entry into the cell for replication. Therefore, it is postulated that TNF α receptor blockers can reduce viral entry into human cells and can reduce organ damage. A clinical trial in China is evaluating the efficacy of adalimumab in COVID 19 patients (ChiCTR2000030089).

Passive immunity with convalescent serum

Convalescent serum with polyclonal antibody products has been used in the treatment of acute infections with cytomegalovirus, hepatitis B, and varicella-zoster. Similar strategies can be considered in the treatment of COVID 19. However, determination of effectiveness and dose in the treatment of COVID 19 are not known at this time and need to be studied extensively before being available for treatment.

In a small observational study of 5 patients requiring mechanical ventilation and getting antiviral medications, administration of convalescent serum led to resolution of fever in 3-4 days, oxygenation improved, and ARDS resolved in 4 patients, 3 patients were weaned off of mechanical ventilation at the end of 12 days. Three patients were discharged, and no mortality observed. The remaining 2 patients remained stable at 37 days.[54] However, this is a small study, and the results may not be generalizable.

Recently, the United States Food and drug administration approved the use of convalescent serum for confirmed COVID 19 patients with a severe or life-threatening disease. The convalescent serum donors should have a laboratory-confirmed COVID 19 or have SARS-CoV-2 antibodies, and they should have complete resolution of symptoms at least 28 days before donating or should have at least 14 after the resolution of symptoms and should test negative for SARS CoV-2. Currently, the convalescent serum can only be used with FDA approval either through a clinical trial or for single patient use in emergent cases.[19]

Development of vaccine

The SARS-CoV-2 virus gains access into the host cells using spike protein. This is essential for pathogenicity, and a vaccine targeting the spike protein is being evaluated.[30] National Institute of health is carrying out animal studies, and a phase 1 human trial has begun in Seattle, WA.[55]

Other medications with in-vitro activity against COVID 19

1) Emetine. Emetine is a protein synthesis inhibitor approved for the treatment of amoebiasis. Emetine has broad antiviral activity against several viruses, including HIV 1, Cytomegalovirus, Ebola virus, and Zika virus.[56-58] In a recent in-vitro study, emetine was able to inhibit the replication of the SARS CoV-2 virus.[40] Nitazoxanide is an antiprotozoal agent approved for the treatment of cryptosporidium and giardia has shown antiviral activity in the in vitro settings.[59] Nitazoxanide upregulates innate antiviral immune response against viral infection through the amplification of RNA sensing and Type 1 interferon response.[60,61] Currently, there are no clinical trials using emetine or nitazoxanide at this time. However, in search of an effective treatment for SARS CoV-2, these antiprotozoal medications should be explored.

2) Homorringtonine. Homorringtonine is a plant alkaloid with antitumor activity by binding to the ribosomal A site and inhibits protein synthesis. Omacetaxine is a semi-synthetic form of homorringtonine approved for the treatment of chronic myeloid leukemia. Homorringtonine is also a broad antiviral agent with activity against Herpes viruses, coronaviruses, hepatitis B, and echoviruses.[62,63] In an in-vitro study, homorringtonine was able to inhibit SARS-CoV-2. This indicates Omacetaxine could be a potential anti-COVID 19 medication that needs further reconsideration.

Prognosis. As previously discussed, nearly 80% of the patients are improving without any significant medical help. Most patients who develop severe diseases likely have a severe respiratory illness, and it is more common among the elderly with poor prognosis. Further, approximately 14% percent of patients will need inpatient hospital admission and intensive care may be required in 2% of the patients with up to 5% mortality.[7] Corticosteroids are the only medications that have shown mortality benefit in the treatment of severe COVID-19. Results from larger randomized control trials may provide us better insights into effective treatment.

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