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# **Review Article**

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# Pharmacologic agents for the management of COVID-19: a review

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# **ABSTRACT**

Coronavirus, in December 2019, caused a SARS-2 pandemic. Primarily targeting the human respiratory system, the major symptoms of this disease are high grade fever, dry cough, shortness of breath, sore throat, and fatigue while symptoms involving other organ systems such as diarrhea, headache, conjunctivitis, and rash also develops. Like a SARS-CoV-1 outbreak in 2002, SARS-CoV-2 is difficult to treat as minimal data is available regarding its treatment strategies and potential cure of the disease. A thorough literature review was done to identify different potential treatments for SARS-CoV-2 and a perspective of a developing country, Pakistan, on managing and treating this infection was provided. We found that use of off-label drugs including including chloroquine, hydroxychloroquine, remdesivir, azithromycin, interferon, ribavirin, lopinavir-ritonavir, increased exponentially to treat COVID-19 patients around the world and studies suggested their efficacy against SARS-CoV-2. Use of adjunctive therapies including convalescent plasma, interferons, and corticosteroids also showed positive results in slowing down the progression of the disease. Different clinical trials are being conducted around the world to identify drugs and develop vaccine against infection caused by this deadly virus. Use of these off-label drugs and adjunctive therapies was also seen in a developing Country like Pakistan, which need desperate measures to overcome COVID-19 disease burden on the country's people and the economy. Coronavirus is infecting thousands of people daily, worldwide. Major action including upgrading medical facilities, investing in health care sector, developing effective drugs, must be taken in both developed and developing countries like Pakistan to fight, contain and prevent future pandemics.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Treatment, Pakistan

# INTRODUCTION

On 31st December 2019, 27 patients with an initial diagnosis of pneumonia of unknown etiology, all epidemiologically linked to Huanan Seafood Wholesale Market were admitted in hospitals of Wuhan city, Hubei province of China. After a few days, Chinese scientists figured out the genomic sequence of etiological agent, using a throat swab samples. This etiological agent proved to be a novel beta coronavirus, now called COVID-19 by the World Health Organization (WHO).<sup>1,2</sup> Although this outbreak is likely to have started from a zoonotic transmission, it soon became clear that efficient person-to-person transmission was also occurring.<sup>3</sup>

As it is one of the major pathogen that primarily targets the human respiratory system, the main symptoms are high grade fever, dry cough, shortness of breath, sore throat, and fatigue while symptoms involving other organ systems such as diarrhea, headache, conjunctivitis, and rash also develops. Apart from these common symptoms, neurological symptoms such as cerebrovascular events, seizures, taste and smell impairment and skeletal muscle injury were also seen especially in patients with severe infection.<sup>4</sup> Invariably, the mode of transmission is through air droplets and direct contact with the affected person but since its involvement of GI tract, it has led many researchers to figure out the possibility of fecal oral route transmission.<sup>5</sup> Although few reports of vertical

transmission from mother to baby have been surfaced but studies have not yet proved such transmission.<sup>6</sup> The median incubation period for severe acute respiratory syndrome coronavirus (SARS-CoV-2) was found to be 5.1 days similar as SARS-CoV-1 and 97.5 % patient developed symptoms in 11.5 days, which implies that a quarantine period of 14 days in suspected cases would potentially expose the infection.<sup>7</sup> The gold standard diagnosis currently recommended by the WHO is nucleic acid amplification diagnostic testing or real time polymerase chain reaction (PCR) of samples collected from suspected patients' nasal and pharyngeal swabs or sputum, or bronchoalveolar lavage.<sup>8</sup> Apart from that, some studies have advised using CT scans of chest which may provide early diagnosis, isolation and management.<sup>9</sup>

From March 2002-July 2003 similar outbreaks of coronavirus (CoV-1), started from China, became a great public health threat caused the similar SARS and the Middle East respiratory syndrome (MERS) with probable 8000 cases and 774 death. A systemic review which was published in 2006 studied clinical trials of different drugs which could inhibit the replication CoV-1 in vitro as well as in vivo and their therapeutic efficacy in treating acute respiratory distress syndrome (ARDS). These drugs include, ribavirin, lopinavir and ritonavir, corticosteroids, type I interferons (IFNs), intravenous immunoglobulin (IVIG), or convalescent plasma (CP). Upon investigating, none of these drugs showed promising effects in treating patients of SARS. Although researchers noticed the vast variations in treatment regimens used in these trials such as wide range of doses, duration of therapy and route of administration that could be a source of obstacle in gaining a fruitful result. In conclusion, this study suggested attempts to develop standardized treatment protocols and to collect and contribute information for a standardized minimum dataset that could facilitate analysis of treatment outcomes among different settings in case of the new outbreak in future.<sup>10</sup>

Globally there are 39,023,292 reported cases of SARS-CoV-2 and out of these patients 1,099,586 have died according to WHO in a report published 16 October 2020. With over eight million cases, United States of America has the highest number of cases in the world.<sup>11</sup>

#### **PATHOGENESIS**

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses consisting of four structural proteins Spike (S), membrane (M), envelop (E) and nucleocapsid (N). Spikes are glycoprotein that are used to enter the host cell by binding to angiotensin converting enzyme 2 (ACE-2) receptor. Expression of this receptor in the lung, heart, ileum, kidney, and bladder results in multitude of symptoms. After attachment, the virus penetrates the cell via endocytosis, replicates in nucleus, makes new viral proteins, and finally releases. <sup>12</sup> In response to this mechanism, the host body increases its production of leukocytes and cytokines. This creates a

proinflammatory state which trigger a violent attack by the immune system to the body resulting in ARDS and multiple organ failure ultimately leading to death.<sup>13</sup>

#### PHARMACOLOGICAL THERAPY

Use of the off-label drugs including chloroquine, hydroxychloroquine, remdesivir, azithromycin, IFNs, ribavirin, lopinavir-ritonavir, and CP increased exponentially to treat COVID-19 patients around the world. These drugs are being used without controls except for few randomized trials in China and US. Off-label use of these drugs can cause rare and serious life-threatening adverse effects including torsades de pointes due to QT interval prolongation, hepatitis, pancreatitis, neuropsychiatric effects, and bone marrow dysfunction. <sup>14</sup>

# Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are widely used drugs in prevention and treatment of malaria and several viruses including members of flaviviruses, retroviruses, and coronaviruses. They demonstrate their antiviral effects by interfering with the endosome-mediated viral entry into the cell or the replication of enveloped viruses through certain processes such as endosomal acidification, proteolytic processing, and inhibiting glycosylation of host receptors. <sup>15,16</sup>

A study conducted in 2003, suggested that SARS, caused by coronavirus (CoV-1), might be treated with chloroquine by inhibiting replication of the causative agent. This, however, was assumed to be its treatment, necessitating a research that could find definitive treatment against coronavirus to prevent new outbreak of SARS.<sup>15</sup> As predicted, a new outbreak of SARS-CoV-2, caused by the same coronavirus, occurred in the year 2019, causing havoc around the world and again focusing on developing a definitive treatment against this virus. Several trials were and are being done to study effectiveness of treating this virus with chloroquine and hydroxychloroquine. A study from China reported that after treating more than 100 COVID-19 patients with chloroquine, progression of the disease slowed down, radiographic findings improved, and virus clearance increased. This study also reported that no significant adverse effects were seen in patients who were given Chloroquine at doses and duration proposed for COVID-19.<sup>17</sup>

As for hydroxychloroquine, an open-label nonrandomized study on 36 patients was conducted in France, in which 20 patients were in hydroxychloroquine group and 16 patients in the control group. This study reported improved virologic clearance in the hydroxychloroquine group patients as compared to the control group and a much superior virologic clearance in patients who were given dual therapy containing azithromycin and hydroxychloroquine than to those who were treated with hydroxychloroquine monotherapy. Another study

conducted on 30 SARS-CoV-2 patients in China, concluded that there was no difference in the virologic outcomes in patients that were treated with hydroxychloroquine to those who received standard care.19 One of the major reasons of this variability in result is smaller sample size, suggesting that a large-scale study must be conducted to show effectiveness of chloroquine and hydroxychloroquine in treating coronavirus.<sup>18</sup>

### Lopinavir/Ritonavir and other Antiretrovirals

Antiretrovirals are a class of drugs that are approved for the treatment of HIV/AIDS. These drugs have shown in vitro to be effective against other novel coronaviruses (nCoVs) via inhibition of 3-chymotrypsin like protease. 20,21 However, limited data is available that shows effectiveness of these drugs against SARS-CoV-2. A study conducted on four patients with mild to severe COVID-19 pneumonia, who were treated with lopinavir/ritonavir, umefinovir (also known as Arbidol), and Shufeng Jiedu capsule (traditional Chinese medicine), showed that three patients gained significant improvement in the COVID-19 pneumonia associated symptoms.<sup>22</sup> A retrospective study conducted on 134 COVID-19 pneumonia patients reported that there was no significant difference in reducing viral load or in improving symptoms between lopinavir/ritonavir-treated group, umefinovir-treated group, and control group.<sup>23</sup> This variation in the results of the studies requires future studies to be conducted on a larger scale to warrant efficacy of lopinavir/ritonavir and other antiretrovirals. Currently, many randomized controlled trails (RCTs) are going on around the world, 13 alone in China, to study effectiveness of antiretrovirals against SARS-CoV-2.<sup>24</sup>

#### Ribavirin and other Antivirals

Ribavirin is an antiviral drug that inhibits viral RNA-dependent RNA polymerase. It is effective against other nCoVs and studies suggest that it had limited in vitro activity of SARS-CoV-1 and requires high doses to inhibit viral replication, making it a possible candidate in treatment of SARS-CoV-2. Hemolytic anemia is the most feared dose-dependent adverse effect associated with the use of ribavirin. <sup>25</sup>

Umifenovir, approved for the prophylaxis of influenza in Russia and China, is an antiviral agent that targets protein/ACE2 interaction, inhibiting membrane fusion of viral envelope.<sup>26</sup> This drug is another possible candidate in COVID-19 treatment due to its in vitro activity against SARS-CoV-1.<sup>27</sup> A study conducted on 67 COVID-19 patients, reported lower mortality rates and higher discharge rates in patients who were treated with umifenovir compared with patients who did not receive this drug.<sup>28</sup> RCTs are going on in China to further establish efficacy of this drug in treating COVID-19 patients.<sup>16</sup>

#### Remdesivir

Remdesivir is a mono phosphoramidate prodrug that is metabolized to analogue of adenosine triphosphate. Its antiviral mechanism is to incorporate into viral RNA and initiate its termination.<sup>29,30</sup> This drug is largely studied due to its therapeutic efficacy against Ebola virus.31 A study conducted in June 2017 demonstrated that remdesivir, GS-5734, inhibited SARS-CoV-1 and MERS-CoV-1 replication in multiple in vitro studies.<sup>32</sup> Knowing its broad-spectrum activity against viruses, researchers during COVID-19 pandemic have orchestrated multiple clinical trial to observe the efficacy and safety of remdesivir in COVID-19 patients.<sup>33</sup> In their prospective cohort study, Grein et el provided remdesivir for 10 days on a compassionate- use basis to patients hospitalized in different countries. Analyzing the results after 18 days, they found out that 36 out of 52 patients i.e. 68% showed clinical improvement and 47% were discharged. Out of many experiments, one randomized control trial, quadruple blinded study has already enrolled 308 participants, giving one group a 200 mg loading dose of remdesivir on day 1, followed by 100 mg IV once-daily maintenance doses for 9 days and placebo with the same dosage to the other group. The primary outcome will be measured in terms of Time to Clinical recovery (TTCR), up to 28 days, which is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalization of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours, or live hospital discharge, whichever comes first.34

On May 1, 2020, FDA authorized the emergency use of remdesivir for treatment of COVID-19 in hospitalized patients.<sup>35</sup>

# Ivermectin

It is a broad spectrum anti parasitic agent but in recent years it has shown antiviral activity in vitro. It has already shown some promising effects against some RNA viruses including dengue virus, zika virus and yellow fever and other, by inhibiting importin  $\alpha/\beta$ -mediated nuclear import (IMPα/β1), terminating replication of virus.<sup>36-38</sup> Being an RNA virus, studies have shown the potential use of IMPα/β1 during infection by SARS-CoV-2 which led many scientists to believe ivermectin as a treatment option.<sup>39</sup> In vitro studies, single dose of ivermectin has been shown to decrease viral load up to 5000-fold within 48 hours. However, increasing time up to 72 hours or increasing dose up to 10-fold greater than recommended by FDA failed to show any further reduction in viral load.40 A paper published by Caly et.al, renders the people in believing it as a treatment of SARS-CoV-2 and started panic buying it despite the authors cautious conclusion that ivermectin "warrants further investigation for possible benefits in humans". 37,41 Generally, considered a safe drug, multiple studies have found a dose dependent neurotoxic effects in rats

invertebrates. These effects accentuate when used in hyper inflammatory state as it results in increased permeability of endothelial cells in blood brain barrier causing more drug to leak into brain.<sup>37,42</sup>

# **ADJUNCTIVE THERAPIES**

# Convalescent Plasma Therapy and Hyperimmune Immunoglobulins

CP therapy and hyperimmune immunoglobulins to treat patients affected with various diseases including H1N1 influenza A, and SARS-CoV-1 was associated with reduction in mortality.16 Its use as an adjunctive therapy for COVID-19 has shown positive results with reduction in the viral load and increase in SARS-CoV-2-specific ELISA and neutralizing antibody titers. This effectiveness was confirmed by a study conducted on 10 severe COVID-19 patients, which reported improvement in clinical symptoms after transfusion of 200ml of CP. A case series of 3 COVID-19 patients in China, treated with high-dose IVIG, antivirals, and steroids, also reported an improvement in clinical status of the patients with no significant adverse effects associated with the use of IVIG.

# Interferons

Type 1 interferons (IFNs-1) are a group of cytokines with antiviral activity that have been effective in treating MERS-CoV1 and SARS-CoV-1. Various studies and clinical trials are being performed to establish effectiveness of IFNs in treating SARS-CoV-2. An observational cohort study was carried out on 36 COVID-19 pediatric patients in which IFN- $\alpha$  was given as a combination therapy with Lopinavir/Ritonavir. All patients were cured after receiving this regimen suggesting a positive role of interferons in treating SARS-CoV-2 patients.

# Corticosteroids and Anti-inflammatory drugs

The role of corticosteroids in treating viral illnesses has been controversial. As an immunosuppressive agent, it reduces the host inflammatory responses but on the other hand its causes delayed viral clearance and increases risk of secondary infection.<sup>16</sup> A retrospective study conducted in Wuhan, China on 201 patients demonstrated that the patients with ARDS who were treated with methylprednisolone were associated with lower mortality rate than those without.<sup>47</sup> Russell et al. gathered clinical evidence from multiple studies and found out that the use of corticosteroids in viral infected patients such as MERS-CoV, SARS-CoV, RSV and influenza were shown no benefit in reducing lung inflammation or mortality and were associated with complications such as diabetes and psychosis related to steroid use.<sup>48</sup> On march 23, 2020, WHO published a second edition providing guidelines for clinical management of suspected cases of SARS-CoV-2, in which due to lack of evidences in support of its benefits, they regarded the use of corticosteroids as harmful and prohibited its supplementation. 49

On the other hand many studies have demonstrated the role of NSAIDS such as diclofenac and ibuprofen in acute respiratory tract infections which have been linked with poor outcomes including complicated pneumonia, pleural effusion, meningitis, quinsy, sinusitis and more. <sup>50</sup> However, these evidence are not enough to eliminate the use of NSAIDS in COVID-19 and some of its beneficial effects for example, relieve of musculoskeletal pain and nighttime symptoms that will improve immunity. Although, it is still not advised to use it a primary therapy while patients of cardiovascular disease who are using aspirin as an antiplatelet drug should continue their treatment. <sup>51</sup>

#### **Immunomodulators**

Some severe cases of SARS-CoV-2 infected patients exhibited a hyperinflammatory state or cytokine storm, which ultimately resulted in ARDS and/or multiple organ failure, the former being the leading cause of death. This state is characterized by increased levels of many cytokines including IL-1, IL-2, IL-6, TNF- $\alpha$  and many others.52 Many studies have shown the adjunctive use of immunomodulators agents with novel therapies to be beneficial especially in severe cases.13 Randomized clinical trials on drugs like anakinra (IL-1 blockade) , tocilizumab (IL-6 receptor blockade) and baricitinib (Janus kinase inhibitor) have shown significant survival benefit in severe cases of pneumonia caused by SARS-CoV-2.  $^{53-55}$ 

# Vitamin D

A well understood vitamin which regulates calcium level in our body, has also been proposed to increase immunity and reduces the risk of viral infection.<sup>56</sup> Understanding its function in reducing common cold, one review study has categorized its mechanism into three main categories: physical barrier, cellular natural immunity, and adaptive immunity.<sup>57</sup> The idea of supplementing vitamin D (vit-D) in reducing the risk of infection comes from the observation of increased incidence of common cold during winters than summers and more severe cases in older patients. In both scenarios low levels of vit-D is a common factor.<sup>56</sup> In the midst of COVID-19 outbreak, many researches have recommended to maintain serum level of 40-60 ng/mL (100-150 nmol/L) of vit-D and administrating an oral loading dose of as high as 50,000 IU (four to six capsules) in patient having low levels of vit-D. Being a natural vitamin, its toxicity is rare. 56,57

# Other possible pharmacologic strategies

By studying virus interaction with host cell in detail, researchers found out some cholesterol rafts on the host cell membrane which facilitates binding of virus with

ACE2 receptor. Macromolecules such as methyl-βcyclodextrin (MβCD) and phytosterols were found to be effective in reducing the infectivity of virus by depleting cholesterol rafts and by dose dependent reduced expression of ACE2.<sup>58</sup> As aforementioned the importance of ACE2 receptor in the pathogenesis of SARS-CoV-1 and also SARS-CoV-2, its role depends upon the cleavage by cellular serine protease TTMPRSS2, inhibitor of which such as camostat mesylate and nafamostat mesylate partially blocked the entry of virus in the host cell.<sup>59</sup> Another study has showed evidence of supplementing essential amino acids specially nicotinamide which would increase antimicrobial peptides. They do so by regulating gut microbiome and maintain host immune system which will ultimately result in less SARS-CoV-2 induced lesions in the intestine.<sup>60</sup>

#### **CONCLUSION**

Coronavirus, in December 2019, caused a SARS-2 pandemic which still is infecting thousands of people daily. With number of people getting affected on the rise, this pandemic has overwhelmed all the medical facilities, the paramedic staff, and doctors and has given a major indication of the shortcomings in health care sector all over the world. With similar pandemic in 2003, different treatment strategies are being employed to treat this contagious infection including the use of off label drugs, antiretrovirals and other antivirals and different adjunctive therapies like CP therapy and IFNs. Major action including upgrading medical facilities, investing in health care sector, developing effective drugs, must be taken in both developed and developing countries to fight, contain and prevent future pandemics.

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