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An Overview the Role of Pharmacology in Managing Post-COVID-19 Complications

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ABSTRACT

Infections caused by severe acute respiratory syndrome coronavirus 2 are alarming globally, resulting in significant loss of life and property. Individuals are confronting a dire pandemic situation due to the lack of suitable medications to address severe acute respiratory syndrome coronavirus 2 infections. This review sought to elucidate the pharmacological interventions implemented globally to combat the COVID-19 pandemic. Drug repositioning is a viable method, with several medications having been repurposed, including lopinavir/ritonavir, remdesivir, favipiravir, and tocilizumab. This research delineates the primary pharmacological characteristics of medicines administered to COVID-19 patients, emphasizing their antiviral, immunomodulatory, and/or anti-inflammatory effects.

Introduction:

Coronaviruses are a category of single-stranded RNA viruses distinguished by their spherical morphology. These viruses can be classified into four subfamilies: α-, β-, γ-, and δ-coronaviruses. γ- and δ-coronaviruses predominantly infect birds, whereas α- and β-coronaviruses primarily infect mammals [1]. β-coronaviruses encompass the severe acute respiratory syndrome coronavirus (SARS-CoV), identified in Guangdong in 2002, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), discovered in Saudi Arabia in 2012. In December 2019, a novel β-coronavirus, SARS-CoV-2, arose in Wuhan, Hubei province, China, where it was identified as the causative agent of the new infection COVID-19 [2]. Following a swift global dissemination of the disease, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Current research indicates that the outbreak originated via animal-to-human transmission [3]. A phylogenetic analysis has revealed that the novel coronavirus exhibits a strong clustering with the sequence of bat SARS-like coronavirus. It possesses envelopes, and the particles are round or elliptical with diameters ranging from 60 to 140 nm [4]. The replication of SARS-CoV-2, like other coronaviruses, commences with the binding to the host cell via interactions between the Spike protein (S protein) and its target protein. During this phase, the virus engages with the ACE2 enzyme, located on the cell membrane's outside, and the serine protease TMPRSS2. Upon entering the cell, the processes of replication and transcription commence [5].

Given the development of effective COVID-19 vaccines, which possess remarkable but not infallible efficacy, and considering the potential emergence of new viral variations that may diminish this efficacy, it is appropriate to shift our focus from prevention to treatment. Furthermore, a significant number of individuals remain unvaccinated. The European Medicines Agency (EMA) authorized the Comirnaty vaccination for children aged 5 to 11 years on 25 November 2021 [6]. The interventions for the condition are starting to yield measurable and substantial results in both direct antiviral therapy and anti-inflammatory and immunotherapeutic treatments.

Review:

In the process of mutation, viruses are continually evolving. During the course of this pandemic, several variations of SARS-CoV-2 have been discovered in different parts of the world. The World Health Organization (WHO) has determined that novel coronavirus variants can be classified into two categories: variants of concern (VOC) and variants of interest (VOI). VOI is defined as "a variant with specific genetic markers that have been associated with changes to receptor binding, reduced neutralization by antibodies generated against previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity" [7,8]. The Centers for Disease Control and Prevention (CDC) defines VOC as "a variant for which there is evidence of an increase in transmissibility, more severe disease (for example, increased hospitalizations or

deaths), a significant reduction in neutralization by antibodies generated during previous infection or vaccination, a significant reduction in neutralization by antibodies generated during previous infection or vaccination, or diagnostic detection failures." These mutations are the reason of the increased amount of SARS-CoV-2 that is capable of being transmitted in the current environment. There is a mutation in the spike protein of the virus that is present in the majority of SARS-CoV-2 types [9]. The process of determining new targets for current pharmaceuticals is referred to as drug repurposing, and it is considered to be an approach that is both efficient and cost-effective. It is predicted that seventy-five percent of the medications that are now on the market might be repurposed to treat a wide range of disorders [10]. Outbreaks of SARS-CoV-2 present doctors with unique challenges when it comes to selecting appropriate pharmacological treatments in a clinical context where there is limited time for the discovery of innovative drugs [11]. The repurposing of existing medicines for the treatment of multiple diseases has recently become a common technique. This is due to the fact that it makes use of risk-free compounds that have familiar pharmacodynamic, preclinical, and pharmacokinetic profiles. These compounds are able to go straight through the late phase of clinical trials, which enables the development of drug processes that are both low-cost and faster [11].

Molecular docking was performed on Ribavirin, Remdesivir, Sofosbuvir, Tenofovir, and Galidesivir in order to investigate their effectiveness against SARS-CoV-2. The results of this study demonstrated that these medications have a higher affinity for binding to the RNA dependent RNA polymerase (RdRp) of COVID-19. These antiviral medicines are anti-RdRp medications, which bind strongly to the RdRp site of COVID-19. As a result, they are proposed for the treatment and management of COVID-19 [12]. Remdesivir was found to be a more effective prospective antiviral medication than Lopinavir and Ritonavir in treating SARS-CoV-2, according to in vitro research and an animal study model. Other antiviral agents, such as Ritonavir, Lopinavir, and Remdesivir, were also investigated for their effectiveness against SARS-CoV-2. On the basis of the pre-clinical data that substantiates anti-viral activity against coronaviruses (SARS and MERS) and the in vitro capability of the agents to inhibit SARS-CoV-2 replication, various medicines such as hydroxychloroquine, azithromycin, ritonavir, ruxolitinib, and camostat were suggested and subsequently moved forward for clinical trials. In addition, other nucleoside and nucleotide analogues, such as sofosbuviralovudine and zidovudine, have been discovered to be effective against the SARS RdRp in in-vitro biochemical tests. These analogues may potentially have the potential to be repurposed for use against COVID19. Over the past few years, there has been a growing interest in the utilization of Remdesivir and Favipiravir as potential treatments for SARS-CoV-2. Currently, clinical trials are being conducted in a variety of countries, including Nepal. The usage of Remdesivir and Favipiravir in the treatment of SARS-CoV-2 has been proven to have considerable benefits, according to studies [13,14].

Remdesivir, which was initially created to combat the Ebola virus, contains antiviral properties that are widespread and effective against a wide variety of RNA viruses. Remdesivir is a nucleotide analogue prodrug that has been reported to have both preventive and therapeutic efficacy against SARS-CoV-2. It is characterized by the inhibitory property of viral RNA dependent RNA polymerase (RdRp), suggesting that

it is effective against the virus. The antiviral activity of Remdesivir was found to be superior to that of Ritonavir and Lopinavir, and it was found to improve pulmonary function, reduce viral load in the lungs, and also diminish numerous lung diseases. In a clinical trial that was carried out at 105 hospitals across the United States, Europe, and Asia, there was a lack of data about the potential efficacy of Remdesivir in patients with moderate COVID-19 who were under treatment for a period of five days.The administration of Remdesivir was associated with an improvement in oxygen-support status among severe COVID 19 patients, according to a smaller number of trials [15]. A randomised, double-blind, placebo-controlled, multicenter experiment was conducted among adults with severe COVID-19 at ten hospitals in Hubei, China. The results of this trial resulted in the surprising discovery that Remdesivir did not provide any clinical advantages. There is no utility of Remdesivir in the treatment of COVID 19 infection, according to a note that was released by the World Health Organization (WHO) [16,17,18].

Remdesivir has been recommended for use in the treatment of COVID-19 in hospitalized adult and pediatric patients who are over the age of 12 and weigh less than 40 kilograms. This recommendation was made by the Food and Drug Administration (FDA). In addition, the Food and Drug Administration has given its approval for the treatment of COVID-19 in hospitalized pediatric patients who weigh between 3.5 and 40 kilograms or who are younger than 12 years old and weigh more than 3.5 kilograms. Similar to the previous example, an observational study that was conducted by the Nepal Health Research Council demonstrated that the usage of Remdesivir resulted in a considerable improvement in COVID patients. According to the findings of the study, the administration of Remdesivir demonstrated a survival rate of 98.4% among patients with mild COVID. In a similar vein, the use of Remdesivir in Nepal resulted in a better outcome for patients with severe COVID, albeit it was associated with a relatively low incidence of adverse effects (4.5%) [19].

Since it is an antiviral medication, favipiravir is widely regarded as the drug of choice for treating influenza virus infections. The influenza virus's RNA-dependent RNA polymerase is inhibited in a selective manner by this substance. Favipiravir has been shown to be effective in treating influenza and the Ebola virus, according to the many pieces of evidence. Patients who were treated with Favipiravir were found to have faster clearance of virus and changing of chest imaging compared to patients who were treated with Ritonavir and Lopiravir, according to the findings of an open label comparative controlled research that was conducted among COVID-19 patients [20]. On day seven, the efficacy of Favipiravir was shown to be lower than that of arbidol in patients with severe COVID-19, according to a study that was carried out in China [21]. On the other hand, it was found to be more effective in patients with moderate COVID-19 than arbidol.

Molnupiravir is a prodrug that originates from the ribonucleoside analog of β-D-N4-hydroxycytidine type. It has been demonstrated that it is capable of inhibiting the replication of a wide range of viruses while exhibiting a low level of cytotoxicity and a high level of resistance. When the active form of a medicine is integrated into the

virus rather than uracil or cytosine during the process of RNA production, it triggers transformations from G to A and C to U in a dose-dependent manner, which ultimately leads to lethal mutagenesis throughout the whole genome of many viruses [22]. Molnupiravir may potentially block SARS-CoV-2-RdRp in a host cell, which is another putative mechanism of action for the drug. This method of action may also hinder viral replication. It has been demonstrated that molnupiravir is effective against influenza as well as a number of different coronaviruses [22].

Among the several anthelmintic activities that it possesses, ivermectin is a macrocyclic lactone. This particular substance is a nuclear transport inhibitor that is aided by the importin αβ/1 heterodimer. This particular heterodimer is accountable for the translocation of viral proteins that are essential for the replication of RNA viruses. Moreover, it protects the S protein, which is responsible for binding to the transmembrane receptor CD147 and ACE-2 [23]. It is possible that the antiviral activity of ivermectin is also related to the allosteric modulation of the P2X4 receptor. P2X4 receptors are cation-selective channels that are gated by extracellular ATP and act as an ionophore. Ivermectin has also been shown to have anti-inflammatory properties in mice, which suggests that it may help reduce the cytokine storm that occurs in COVID-19. A study conducted by Caly and colleagues found that ivermectin suppresses the multiplication of SARS-CoV-2 in vitro [24].

Niclosamide is a medication that has been tested and authorized for the treatment of tapeworm invasion. The mechanism of action involves the inhibition of S-phase kinase-associated protein-2 activity through the promotion of autophagy, which ultimately leads to a reduction in the replication of coronavirus. Another possible target of this mechanism is the SARS-CoV-2 virus. It has been demonstrated that niclosamide is capable of inhibiting SARS-CoV-2 at the submolecular level. According to the findings of a clinical investigation, niclosamide has been demonstrated to reduce the severity of cytokine storms in patients with severe COVID-19 [25].

It has been determined that tocilizumab is effective in treating rheumatoid arthritis as well as cytokine release syndrome. The humanized recombinant monoclonal antibody (mAb) is a type of antibody that binds to the human IL-6 receptor (IL6R) and disrupts the signal transduction pathway that it is responsible for. Through the inhibition of the IL6R, it reduces the levels of proinflammatory cytokines that are elevated in the presence of severe COVID-19 circumstances. When tocilizumab was administered to a patient with COVID-19 and multiple myeloma, the patient made a full recovery, according to a study that was conducted in China [26]. In addition to receiving various therapies, such as lopinavir-ritonavir, a patient from France who was 42 years old and suffering from respiratory failure caused by COVID-19 saw rapid and positive outcomes following the administration of tocilizumab through intravenous infusion. Patients diagnosed with critical COVID-19 were the subjects of a study that investigated the efficacy of tocilizumab [27]. Tocilizumab was suggested for treatment in critical patients, such as those suffering from pneumonia or those who are being ventilated, according to a clinical research conducted in Italy [28].

Medications that are classified as corticosteroids, such as hydrocortisone and dexamethasone, have been linked to a reduction in fatality rates in viruses such as

influenza A. When compared with patients of COVID 19 who were receiving the standard treatment, it has been found that dexamethasone was able to improve death rates in severe COVID-19 patients who required mechanical breathing [29]. When administered to COVID-19 patients who did not require breathing help, dexamethasone did not result in any improvement in the death rate. They have anti-inflammatory qualities that can assist to reduce the amount of systemic inflammation, reduce the amount of fluid retention in the lungs, and prevent additional alveolar injury, which ultimately leads to an improvement in hypoxia and a reduction in the risk of respiratory system failure [29].

It is possible to acquire immunoglobulins and convalescent plasma (CP) from individuals who have recovered from Coronavirus infection-19. Plasma should be collected from donors no sooner than the second or third week following SARS-CoV-2 infection [30]. This is due to the fact that the predominant immunological response of the host manifests itself 10 to 14 days after infection. Plasma would give passive protection based on antibodies, and as a result, it might lessen both the intensity and length of the disease. As a result, it could be indicated in patients who are hospitalized, with a particular focus on immunosuppressed patients who have insufficient antibody generation. Plasma transfusion is a human blood product that has the potential to induce the same reactions as transfusions, including allergic and anaphylactic reactions, hemolysis, and fluid overload, among other conditions. However, studies have consistently demonstrated that plasma transfusion is safe and has effects that are comparable to those of regular transfusions [31]. The basis for its use, the experience in prior viral epidemics, and the fact that it is safe are all factors that have contributed to the fact that there are still no clear outcomes in terms of its effectiveness. The publishing of observational studies and clinical trials [31], along with systematic reviews and meta-analyses, which have produced ambiguous results, marked the beginning of its application in the treatment of moderate-to-severe COVID-19. Furthermore, these trials were different from one another in terms of the features of the convalescent plasma that was utilized (for example, in terms of the amount of antibodies present and the stratification of recipient patients according to their serological status).

Given these findings, the Food and Drug Administration (FDA) argued that a "totality of evidence" suggested that the benefits of convalescent plasma would outweigh its risks. Furthermore, given the lack of effective treatments, the FDA granted an Emergency Use Authorization (EUA) and provided guidance on the manufacture and use of convalescent plasma in hospitalized patients who exhibited signs of progressive infection [32].

Conclusion:

The COVID-19 pandemic remains a worldwide concern. Despite the remarkable news of millions obtaining safe and effective immunizations daily, the novel coronavirus will persist in spreading until global herd immunity is attained a goal that may require considerable time to realize. Public health experts must remain vigilant for viral mutations. We will be able to properly manage future incidents if we own a variety of

dependable therapeutics in our COVID-19 arsenal. According to the USFDA's CTAP, antiviral medicines, steroids, cell and gene treatments, and monoclonal antibodies are among the medications that may effectively treat COVID-19. Significant global efforts have been undertaken over the past year to discover suitable medications and vaccines for COVID-19. Certain vaccinations and medications have received Emergency Use Authorization based on initial results by the government and are being utilized to combat COVID-19 infection. Remdesivir and molnupiravir are antiviral agents with distinct modes of action that have shown success in clinical studies across many indicators of disease progression. Currently, following extensive published data, convalescent plasma cannot be regarded as a therapy of proven efficacy for patients with COVID-19 in any clinical context. Monoclonal antibodies, both commercially available and under development, reduce the progression to severe types of the disease when injected early in its natural course. Certain monoclonal antibodies currently under development may, contingent upon established efficacy, be delivered preventively and provide long-term effects.The function of dexamethasone in critically ill individuals with COVID-19 is well established. The comparative efficacy of different corticosteroids at equal dosages is less definitive. Dexamethasone is not indicated for use in less severe conditions. Other immunomodulatory agents with distinct mechanisms of action are already indicated for individuals with severe pneumonia and respiratory failure.

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