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REVIEW ARTICLE

Drug Development Strategies and Immunological Aspects of SARS-CoV-2

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Abstract:

Following the 1918 influenza virus attack, which resulted in a worldwide pandemic, the world is again facing a similar situation as of March 2020, according to the World Health Organization (WHO). The discovery of a novel infectious agent from the Coronaviridae family was made possible by advancements in Medical Science and achievements in pharmaceutical research. SARS-CoV-2 is a member of the coronavirus family, a large and diverse group of viruses with a wide range of characteristics. This single-stranded RNA virus that infects humans and other animals has a single linear RNA segment and infects them in a positive-sense manner. The common cold is not the only sickness that coronaviruses may cause. They can also cause more dangerous infections like the Middle East respiratory syndrome (MERS), with a 34 percent mortality rate. Rapid sequencing by several organizations aided in identifying the virus's structure and function, determining the virus's immunogenicity in various populations, and developing effective prophylactic medicines for the virus. As of December 2020, the Centers for Disease Control and Prevention (CDC) announced that more than 150 vaccine candidates for COVID-19 were developing. Because of this, a total of 52 potential vaccination candidates are now being investigated in different phases. According to the WHO, nine vaccines have been approved and have extensive use from at least one regulatory authority, and five more are under evaluation.

Keywords: Immune response, Drug repurposing, SARS-CoV-2, Angiotensin-converting enzyme 2, Levamisole, Niclosamide, Sitagliptin, Favipiravir.

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1. INTRODUCTION

As a result of coronavirus entering the host cell through the angiotensin-converting enzyme 2 (ACE2), prevalent in type II alveolar cells of the lungs, it is presumed that it preferentially targets respiratory receptors [1, 2]. It seems that the existing therapeutic antibodies might lose protective benefit against the recent B.1.1.529 (Omicron) variant in comparison to others like the B.1.1.7 (Alpha), B.1.351 (Beta), B.1.1.28 [P.1, Gamma]), and B.1.617.2 (Delta), while the other variants require both the ACE2 and TMPRSS2 proteins to inject their genome into a cell, and the new Omicron variant binds only to ACE2 [3].

Pneumonia and lymphopenia are among the most common complications experienced by people who have been infected with the virus. Proteins like spike and nucleocapsids stimulate the host's immune system, resulting in the virus's death [1, 4].

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B cells can produce antibodies in response to viral antigens during the acute phase of infection. After being transported to T cells through MHC complexes, these antibodies stimulate antibody production, increased cytokine release, and cytolytic activity [4]. Because MHC has genetic polymorphisms, it can present specific T-cell surface antigens more efficiently than other MHC alleles when specific T-cell surface antigens are present. Individuals infected with SARS-CoV or MERS-CoV can recover and generate a large memory T-cell pool resistant to the virus, resulting in significant protective responses [4]. However, because of cross-reactivity with other cells in the body, when these memory T cells were triggered, they produced local damage, which resulted in an autoimmune reaction [5]. When exposed to high levels of viral infection, SARS-CoV-2 appears highly contagious and manifests itself in three stages, each with a distinct set of symptoms [6]. It also appears to cause a depletion of the T-cell pool when exposed to high levels of viral infection [4, 6].

Diverse strategies target the identification of efficient

coronaviruses antiviral drugs, including the empirical testing of known antiviral drugs, large-scale phenotypic screening of compound libraries, and target-based drug discovery [7]. Despite its controversial clinical side effects, Remdesivir is the only antiviral FDA drug approved for treating COVID-19 requiring hospitalization [7]. Furthermore, there are additionally approved under an emergency use authorization (EUA) drugs from the FDA like the SARS-COV-2-targeting Monoclonal Antibodies (Casirivimab and Imdevimab, Sotrovimab, Bamlanivimab, and Etesevimab), immune modulators (Baricitinib, Actemra), Sedatives (Propofol-Lipuro 1%, Fresenius Kabi Propoven 2%) and Renal Replacement Therapies (Regiocit replacement solution, Fresenius Medical multiFiltrate/multiBic/multiPlus replacement solutions) [8].

While there is a scarcity of specialized COVID-19 therapy, patients are given various small molecular drugs that are now used to treat SARS, MERS, HIV, Ebola, malaria, and tuberculosis, among other illnesses. The FDA has approved some of these drugs for clinical trials, and more trials are expected to be approved shortly. In addition, retrieved patient plasma in a regular immunotherapy regimen has also been developed to neutralize viremia in COVID-19 patients who have exhausted all other therapeutic alternatives [1, 9].

1.1. A Brief History and Reservoir of the Virus

In December 2019, researchers in the Chinese city of Wuhan identified this year's novel coronavirus, which was dubbed the “2019 novel coronavirus” (2019-nCoV) [10, 11]. Additionally, the virus has been linked to pneumonia and, in some instances, an increased risk of progressive respiratory failure resulting from alveolar damage. Fever, dry cough, dyspnea, and headaches have been reported as the most common symptoms [12]. The virus was genetically analyzed and genetically identical to the SARS-CoV strain responsible for the 2002 and 2003 outbreaks. As a result, the virus was renamed SARS-CoV-2 in February 2020 to emphasize this connection. Acute respiratory distress syndrome (ARDS) can be caused by several viruses, including SARS-CoV, MERS-CoV, and other CoV infections and severe COVID-19 infection ARDS [13]. Proinflammatory cytokines are produced at dramatically increased levels in patients with ARDS [11, 14 - 16]. An excessive release of cytokines results, which is considered a contributing cause in multiorgan failure and greater death rates in the general population. In extreme situations, the disease can have pathophysiological consequences for the heart, kidneys, liver, and central nervous system, depending on various circumstances, including past diseases and immune system responses [17, 18]. Acute illness can have various other adverse effects on the body and its pathophysiological effects on the lungs. Arrhythmias, an increased risk of myocardial infarction, liver dysfunction, and kidney failure are only a few potential side effects, including neurologic symptoms such as ataxia, seizures, neuralgia, acute cerebrovascular illness, and encephalopathy [2, 6]. The virus that causes SARS-CoV-2 can infect tissues other than the lungs, and it is expected that the disease will worsen in these tissues if it does [19].

Based on genomic and phylogenetic analyses [4, 6], the coronaviruses SARS CoV, MERS CoV, and SARS CoV-2 have been identified as zoonotic infections caused by coronaviruses that can spread to humans either directly or indirectly *via* an intermediate host. It is believed that bat coronaviruses, most likely transmitted from bats to humans through direct contact with bats, are the source of a wide range of diseases. Since there is a lack of available data on viral sequences in these animals, determining the likely zoonotic potential of newly identified viruses is extremely difficult to predict. According to a few studies, the SARS-CoV-2 virus spreads more rapidly than the SARS or MERS viruses [20]. All three viruses are widely transmitted in nosocomial settings and exhibit symptoms that are similar to one another. Asymptomatic patients must be closely examined frequently to guarantee that viral shedding does not occur before the onset of clinical signs and symptoms [21, 22]. Researchers have discovered that the presence or absence of signs and symptoms in the transmission of infectious viruses considerably enhances the pandemic potential of an infectious virus [23]. According to WHO, it was declared a pandemic by the World Health Organization on March 11, 2020, due to the rapid and exponential increase in the number of illnesses and fatalities associated with COVID-19 over such a short period of data. Over 10 million disease cases will have been documented worldwide by June 2020, with more than 500,000 people dying due to sickness by that time [24], and now there have been 251,788,329 confirmed cases of COVID-19, including 5,077,907 deaths, reported to WHO. As of November 10, 2021, a total of 7,160,396,495 vaccine doses have been administered [25]. The treatment options for COVID-19 are limited to FDA-approved antiviral or EUA drugs. At the same time, simultaneously, many SARS-CoV-2 vaccines are now being studied and assessed in clinical studies, and others are already approved. In a clinical phase 3 trial using COVID-19 [26], researchers discovered that Remdesivir, an experimental drug originally designed as an RNA-dependent RNA polymerase (RdRP) inhibitor against the Ebola virus (EBOV), proved effective [27]. It was initially intended as an RNA-dependent antiviral treatment when Remdesivir was developed as an investigational medicine. According to researchers from the University of California, people admitted to the hospital with COVID-19 and administered remdesivir had a 31 percent shorter recovery time than those who were not given remdesivir during their hospitalization (from 15 to 11 days) [28]. The Food and Drug Administration (FDA) of the United States declared on May 1, 2020, that Remdesivir had been approved for the treatment of COVID-19, even though formal approval had not yet been issued.

1.2. COVID-19 Infection and Treatment Strategies

A simple cleaning with soap or detergent, on the other hand, would immediately eradicate the COVID-19-causing SARS-CoV-2 virus [16]. The virus may live in aerosols for several hours and on surfaces such as stainless steel, plastic, and cardboard for several days [16]. If the virus can propagate during the time of asymptomatic incubation (expected to occur in 50–60 percent of cases), it can be disseminated for up to two weeks after the beginning of symptoms [29]. According to the Centers for Disease Control and Prevention (CDC), three other

people get infected for every sick individual. Incubation time in a laboratory setting is usually 5–6 days (with a range of 1–14 days). Clinical indicators can range from asymptomatic infection to mild disease to severe or fatal sickness; thus, knowing the whole range of possibilities is crucial [29, 30]. When comparing severe to moderate cases, some estimates suggest that the viral load in individuals with severe symptoms could be up to 60 times higher than in people with mild symptoms. According to medical authorities, pneumonitis and possibly hyper inflammation linked to cytokine storm syndrome are the leading causes of death [12, 18, 21, 31].

Fever and chills were the most prevalent COVID-19 symptoms in Europe (49 percent), followed by dry or productive cough (24 percent), sore throat (12 percent), overall weakness (8 percent), discomfort (7 percent), and then rhinorrhoea (4 percent) and diarrhea (4 percent) (2 percent). Myopathy of the heart, thrombosis of the blood vessels in the brain, and encephalitis are all possible complications [30]. Immunosuppression and other risk factors, including aging and a minority ethnic background, are linked to an increased risk of severe disease and mortality [12, 16]. COPD, cardiovascular disease, hypertension, and other comorbidities, including diabetes, are also strong predictors of critical care admission [12, 30].

The latest studies reveal that mild SARS-CoV-2 infection could be associated with physiological immuno-thrombosis and controlled by body homeostatic mechanism, while in severe cases, uncontrolled physiological immuno-thrombosis may be controlled, extended and developed into pathological immuno-thrombosis [32, 33].

The virus's affinity for ACE2, expressed by epithelial cells in the lungs, colon, kidney, and vasculature, among other sites, is most likely to blame for these risk factors [31]. ACE2 expression is higher among older people, smokers, and individuals with diabetes or hypertension, many of whom use ACE inhibitors, GLT-1 inhibitors, or ibuprofen, compared to the general population [34]. According to two recent Italian and American studies [35], taking an ACE inhibitor or angiotensin II-receptor blocker (or any other single antihypertensive medicine) is not linked to a higher risk of COVID-19 infection, severe symptoms, or death. However, as a result of the evidence, an increased risk of cardiovascular disease has been established, implying that the correlation is causal.

There is little evidence linking NSAIDs/ibuprofen to COVID-19 susceptibility or worsening of symptoms, according to the most recent advice from the Commission for Human Medicines [36]. Patients can self-medicate for COVID-19 symptoms with paracetamol or ibuprofen if they are regularly taken in prescribed amounts. However, additional difficulties may occur, and NICE's brief evidence summary (ES23) [37] summarises all information that is currently available on the subject.

In addition to its antihelminthic effects, niclosamide (NCL) also has pleiotropic anti-inflammatory and antiviral qualities, making it a frequently used medicine in treating a broad spectrum of illnesses. It is thought that NCL affects human biological processes by controlling uncoupling, oxidative phosphorylation, and several signaling pathways. The broad-spectrum antiviral activity of NCL suggests that it may be a potential therapy option for the present pandemic SARS-CoV-2 infection. It may also effectively reduce the severity of COVID-19 infection in some cases [38].

According to a recent study, the SARS-CoV-2 virus uses the enzyme dipeptidyl peptidase 4 (DPP4) as an entrance site into various organs that carry these receptors [39]. In addition to its anti-inflammatory and antioxidant properties, DPP4 inhibitors (also known as gliptins, such as sitagliptin) have been shown to assist patients with type 2 diabetes. These effects have been shown to help reduce inflammation and oxidative stress in diabetic COVID-19 patients. Furthermore, increased levels of dipeptidyl peptidase 4 were discovered in patients with COVID-19 who did not have diabetes, which has been identified as a potential positive effect of sitagliptin in the therapy and management of this condition [40].

Favipiravir is effective against viruses that cause hemorrhagic fever and encephalitis, both life-threatening diseases. Rotaviruses, filoviruses, bunyaviruses, flaviviruses, and filoviruses are examples of viruses that fall within this category. Because many viruses do not have vaccines or antiviral drugs approved by the FDA, discovering effective antiviral therapeutics with a broad spectrum of activity is essential. Unlike other known influenza antivirals, which hinder virus movement both within and outside cells, favipiravir works by impeding virus movement within cells. In addition, prodrugs are modified *via* phosphorylation and ribosylation. Finally, a conversion step is performed to transform the medicine into its active form, favipiravir-RTP, which is effective against HIV. In its active form, Favipiravir-RTP inhibits the transcription and replication of the RNA-dependent RNA polymerase (RDRP (RdRp). This interferes with virus genome transcription and replication, resulting in a decrease in virus activity. Given favipiravir's novel mechanism of action, particularly in viral infections, it is critical to concentrate on the drug's efficacy, dosing regimen, and interactions with other drugs [41 - 43] (Table **1**).

Table 1. Drug repurposing against COVID-19 [45].

Compound	Acting on the	Molecular Formula	Clinical Phase	Ref.
Remdesivir	Virus	$C_{27}H_{35}N_6O_8P$	Trial to Determine the Efficacy/Safety of Plitidepsin vs. Control in Patients With Moderate COVID-19 Infection, Phase 3	[46]
Favipiravir	Virus	$C_5H_4FN_3O_2$	Trial to Determine the Efficacy/Safety of Plitidepsin vs. Control in Patients With Moderate COVID-19 Infection, Phase 3	[47]

(Table 1) contd.....

Compound	Acting on the	Molecular Formula	Clinical Phase	Ref.
Darunavir	Virus	$C_{27}H_{37}N_3O_7S$	Adaptive Randomized trial for therapy of COrona virus disease 2019 at home with oral antivirals, Phase 3	[48]
Ribavirin	Virus	$C_8H_{12}N_4O_5$	Pembrolizumab With or Without Elbasvir/Grazoprevir and Ribavirin in Treating Patients With Advanced Refractory Liver Cancer, Phase 2	[49]
Lopinavir	Virus	$C_{37}H_{48}N_4O_5$	A Study of Combination Therapies to Treat COVID-19 Infection, Phase 2 Withdrawn	[50]
Ritonavir	Virus	$C_{37}H_{48}N_6O_5S_2$	EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High-Risk Adults With COVID-19, Phase 3	[51]
Arbidol	Virus	$C_{22}H_{25}BrN_2O_3S$	Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus, Phase 4	[52]
Azithromycin	Virus	$C_{38}H_{72}N_2O_{12}$	Randomised Evaluation of COVID-19 Therapy, Phase 2/3	[53]
Nitazoxanide	Virus	$C_{12}H_9N_3O_5S$	Trial to Evaluate Efficacy and Safety of Nitazoxanide in the Treatment of Mild or Moderate COVID-19, Phase 3	[54]
Ivermectin	Virus	$C_{48}H_{74}O_{14}$	Randomized placebo-controlled clinical trial evaluating the safety and efficacy of ivermectin in hospitalized patients with COVID-19 disease, Phase 3	[55]
Chloroquine	Host	$C_{18}H_{26}ClN_3$	COVID-19: addition of azithromycin to chloroquine treatment, Phase 4	[56]
Dexamethasone	Host	$C_{22}H_{29}FO_5$	Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe Hypoxia, Phase 3	[57]
Ruxolitinib	Host	$C_{17}H_{18}N_6$	Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS, Phase 2	[58]
Baricitinib	Host	$C_{16}H_{17}N_7O_2S$	Randomised Evaluation of COVID-19 Therapy, Phase 2/3	[59]

Within a year of their introduction, several vaccines are available for distribution. According to the WHO, nine vaccines have been approved and have extensive use from at least one regulatory authority (Pfizer–BioNTech, Oxford–AstraZeneca, Sinopharm BIBP, Moderna, Janssen, CoronaVac, Covaxin, Novavax, and Medicago), and five more are under evaluation (Sputnik V, Sinopharm WIBP, Convidecia, Sanofi–GSK and SCB-2019) [60].

Levamisole (LVM) is an antihelminthic medication that increases the type 1 immune response. These findings imply that LVM could help prevent and treat SARS-CoV-2 infections. Latest studies demonstrated that LVM might be used to treat SARS-CoV-2 and COVID-19 infections in humans [44]. LVM has been linked to a reduction in SARS-CoV-2 replication by blocking a papain-like protease, according to several investigations (PL-pro). This is because LVM activates glucocorticoid receptors in the kidney (AKI). LVM has a strong immune system stimulant impact, affecting cellular and humoral immune responses. Early in COVID-19, this influence is good, but later on, it is unfavorable. SARS-CoV-2 clearance and tissue healing are boosted by early immune activation, whereas late activation increases the risk of cytokine storm amplification. Finally, LVM therapy had a mixed effect on COVID-19, initially favorable but eventually deleterious. Clinical trials and prospective research are needed to prove LVM's efficacy and timeliness in treating COVID-19 [44].

Without question, the most effective technique for COVID-19 disease prevention is a good immunization campaign. However, there are a few key aspects to consider. First, both SARS-CoV and MERS-CoV are under ten years old, and neither has been around for more than twenty years. Second, the FDA has yet to approve vaccines for these diseases, although several promising prophylactic techniques are in the works. Malaria, HIV/AIDS, Ebola, and Zika virus are just a handful of infectious diseases for which no effective vaccinations are available (Zikavirus). Third, vaccine development can take ten to fifteen years and is quite expensive [22, 61, 62].

Furthermore, fast changes in viral RNA may render these vaccines ineffective. RNA viruses change rapidly [63, 64]; however, the S protein amino acid residue sequences of emerging SARS-CoV-2 variants from different countries do not appear to differ considerably [61]. According to preliminary evidence, vaccine-induced antibodies increase the prevalence and severity of disease during subsequent host-pathogen interactions [62]. Antibodies that aid the virus rather than the host are created in a process known as antibody-dependent enhancement (ADE). This strategy allows the virus to benefit more than the host by speeding up viral entry and reproduction in the target cell [63]. Despite identifying ADE in dengue, HIV, respiratory syncytial virus, and influenza virus infections [62], there have been no confirmed instances of SARS or EBOV.

CONCLUSION

The drug repurposing management of SARS-CoV or MERS-CoV consists of new approaches, including compound identification, compound acquisition, development, and FDA post-market safety monitoring [65]. As Boopathi *et al*. summarize [66], the novel computational and experimental models target specific mechanisms against the Covid -19: 1) To elucidate the role of E-protein ion channel activity in virus pathogenesis [66] 2) To identify inhibitor block the E-protein ion channel activity and inhibits COVID-19 RNA polymerase [66] 3) To study the energetic binding affinity of COVID-19 Mpro with new inhibitors based on free energy calculations [66] 4) To investigate the structural properties of the COVID-19 Mpro and study interaction patterns between virus and membrane, virus and inhibitor [66] 5) To monitor the thermodynamics properties of COVID-19 Mpro in the presence/absence of the antiviral inhibitor [66] 6) To develop an effective drug targeting to inhibit the contacts between N-protein and single positive RNA strand to stop viral replication

and transcription [66] 7) To characterize mechanical profile and energetic affinities between Spike (S) protein and ACE2 to boost vaccine developments [66].

Infection control practices have become well established with the virus's similarities to other coronaviruses and recent outbreaks. Existing and new advanced computational technologies can be utilized to expedite the development of novel vaccines and therapies.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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