JABET
Journal of Advanced Biotechnology and Experimental Therapeutics

MINI-REVIEW

J Adv Biotechnol Exp Ther. 2022 Jan; 5(1): 241-246
eISSN: 2616-4760, https://doi.org/10.5455/jabet.2022.d111
Published by www.bsmiab.org

COVID-19 drugs: A necessary strategy for living with COVID-19 in the new normal and the mutations of the SARS-CoV-2 such as omicron variant

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Academic editor
Md Jamal Uddin, PhD
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Article info
Received: 17 August 2021
Accepted: 30 December 2021
Published: 17 January 2022

Keywords
COVID-19 drugs; the new normal; SARS-CoV-2 mutation ; COVID-19 treatment; omicron

ABSTRACT

The COVID-19 pandemic has spread rapidly and caused significant damage to global public health as well as the economy. While the race of vaccine development witnessed a spectacular breakthrough with the introduction of highly effective vaccines such as BNT162b2, mRNA-1273, or AZD1222, no specific drug for COVID-19 treatment has been discovered yet. Recently, repurposing drugs classified into three main groups of mechanisms, including antivirus, anti-SARS-CoV-2 antibodies, and immunomodulators, are investigated. As a result, Remdesivir and six other drugs are authorized by the Food and Drug Administration (FDA) to treat patients infected by the SARS-CoV-2. This work aims to highlight that, besides vaccines, COVID-19 drugs should get more attention and be considered as one of the most promising strategies to safely coexist with the SARS-CoV-2 virus in the new normal status and for the mutations of the virus, such as the omicron variant.

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INTRODUCTION

The global pandemic, the COVID-19, has caused 279,114, 972 confirmed cases and 5,397,580 deaths worldwide (data taken on December 27, 2021) [1]. Since then, the race of vaccine development has never observed a more spectacular breakthrough in the COVID-19 pandemic. A variety of COVID-19 vaccines with their high efficacy, including BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), Sputnik V, and AZD1222, were introduced after only one year of investigation [2]. In contrast, no specific treatment for COVID-19 has been announced yet, although being applied to cutting-edge technologies, including machine learning or artificial intelligence. Therefore, this review will summarize the status of COVID-19 drug development to propose the new strategies for COVID-19 treatment using newly developed drugs for the normal and the mutated SARS-CoV-2 virus, such as the omicron variant.

THE DEVELOPMENT AND STATUS OF DRUGS FOR COVID-19

De novo drug discovery is a high-cost and risky procedure, and usually takes at least 10 years to reach patients. Due to globally urgent demand for an effective COVID-19 treatment, drug repurposing is widely evaluated as a reasonable alternative for traditional drug development. This strategy recognizes a new indication related to COVID-19 treatment for existing drugs. Drug repurposing significantly saves time and

cost thanks to the available pharmacokinetic and safety profiles as well as dosage forms of drug candidates.

Much research for drug repurposing has been published with several approaches [3] including computational studies, *in silico* experiments, and clinical trials [4, 5]. In computational research, disease-based and target-based processes are the main approaches to indicate a new application for the approved drug. Disease-based process means comparing the similarities and characteristics of diseases, while in target-based process, researchers establish the interaction between drug and a list of targets. Computational and *in silico* studies are valuable for initially screening out drug candidates that effectively suppress COVID-19 progression for further clinical trials [6]. Besides, related to clinical trials, there are 7219 studies about COVID-19 therapeutic treatment registered on ClinicalTrials.gov by the time this review is edited **(**December, 2021**).** Of 3573 studies about drugs, the vast majority are in Phase 2 and Phase 3, with nearly 1857 drug interventions.

Summarizing from the three above approaches, currently proposing drugs for COVID-19 could be classified into three main groups based on their mechanisms, including antiviral drugs, human antibody products, and immunomodulators (Table 1). SARS-CoV-2 is a single RNA-strand virus targeting human cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors by spike protein. After fusion, released viral RNA is translated into polypeptides, including structural and nonstructural proteins. A new RNA strand is synthesized through viral RNA-dependent RNA polymerase (RdRp), and the virus is then assembled and successfully replicated. During the life cycle of the SARS-CoV-2 virus, researchers focus on several specific therapeutic targets (Figure 1) [7]. For example, Lopinavir and Darunavir suppress proteolysis via inhibiting 3-chymotrypsin-like protease, while Remdesivir and Favipiravir target viral RdRp to reduce viral replication. Other antiviral drugs like Chloroquine and Hydroxychloroquine inhibit virus fusion into human cell membranes by increasing the pH of endocytosis [7, 8]. Several monoclonal antibodies, such as Sotrovimab, Casirivimab, or Bamlanivimab targeting viral spike protein, are suggested to block viral invasion and show clinical benefits in COVID-19 treatment. Notably, Bamlanivimab was reported to significantly reduce its activity on *beta* and *gamma* variants [8]. This finding raises concerns about resistant viruses that some variants can adopt mutations to reduce their susceptibility to monoclonal antibodies.

Systemic inflammation and cytokine storm are major factors leading to multiple organ failures and death. While corticosteroids, especially dexamethasone, are shown to be effective in suppressing inflammatory responses, several immunomodulators are utilized in combination with dexamethasone to inhibit cytokine storm and give beneficial clinical outcomes, like Tocilizumab, Sarilumab, or Baricitinib [8]. Of many existing drugs belonging to the 3 groups mentioned above, only Remdesivir was approved by the Food and Drug Administration (FDA) to treat COVID-19 disease. Drugs declared in the Emergency Use Authorization (EUA) list should be cautiously used despite being recommended by the FDA and National Institutes of Health (NIH) Panel. The remaining drug candidates are advised against using or still need more randomized trials to conclude [8, 9].

Table 1. Summary of FDA-authorized COVID-19 drugs (up to Sep, 2021) [8, 9, 11]

Group	Drugs	Therapeutic indication	Administration	Mechanism
Antiviral drug	Remdesivir	- Hospitalized patient (≥12 years old & ≥ 40 kg of weight) - Hospitalized pediatric patient (3.5 kg to < 40kg of weight or < 12 years old & ≥ 3.5 kg of weight)	IV 200mg on the first day, 100mg daily for the next 9 days	- Inhibits RNA replication through binding to viral RdRp
Antibody	Casirivimab + Imdevimab	- Mild to moderate patient (≥12 years old & ≥ 40 kg of weight) Patient with high risk of progressing to severe COVID-19 (Bamlanivimab + Etesevimab is not used where their resistant rate exceeds 5%)	Treament/post-exposure prophylaxis 600mg + 600mg, single IV infusion /subcutaneous injection	- Recombinant monoclonal Abs - Bind to spike protein's nonoverlapping epitopes of SARS-CoV-2 virus to block its entry
	Sotrovimab		500mg, single IV infusion	- Bind to the spike protein's epitope conserving between SARS-CoV-2 and SARS-CoV virus to block its entry
	Bamlanivimab + Etesevimab		Treament/post-exposure prophylaxis: - 700mg + 1400mg, single IV infusion	- Neutralizing monoclonal Abs - Bind to different spike protein's overlapping epitopes of SARS-CoV-2 virus to block its entry
	High-titer COVID-19 convalescent plasma	- Hospitalized patient in early stage of disease - Patient with impaired immune system	Initially with 1 unit (about 200mL) - Additional units are based on medical judgment and clinical response	- Contains Abs to SARS-CoV-2 virus from patients who recovered from COVID-19
Immune system modulator	Corticoid (Dexamethasone)	- Patient requires oxygen support	6mg dexamethasone or equivalences - IV/PO once daily	-Anti-inflammatory
	Tocilizumab	- Hospitalized patient (≥ 2 years old) receiving systematic corticoids and requiring supplemental oxygen support	<30kg of weight: 12mg/kg ≥30kg of weight: 8mg/kg - Single IV infusion	- Anti-interleukin-6 receptor monoclonal Abs, suppress interleukin-6 level
	Baricitinib	- Hospitalized patient (≥ 2 years old) receiving systematic corticoids and requiring supplemental oxygen support	2 - < 9 years old: 2mg ≥ 9 years old: 4mg - PO once daily	- JAK inhibitor, prevents the phosphorylation of STAT proteins, which induces immunosuppression - Antiviral effect via interfering viral endocytosis

COVID-19 DRUGS AS A NECESSARY STRATEGY FOR THE NEW NORMAL AND THE MUTATION OF THE SAR-COV-2 VIRUS SUCH AS OMICRON VARIANT

Since its first outbreak in Wuhan in December 2019, the COVID-19 pandemic has rapidly spread to 223 countries and territories globally, with more than 225 million confirmed cases and nearly 5 million deaths [1]. Effective strategies are urgently required to minimize the great pressure COVID-19 puts on global public health. New case detection, general prevention methods, and quarantine are proven effective. However, they can only be utilized as contemporary plans due to their devastating impacts on the global economy and society. Therefore, vaccines and drugs for COVID-19 are always of paramount importance to battle against the SAR-CoV-2 virus for long-term.

Due to the rapid mutation and spread of the SARS-CoV-2 virus, governments and scientists should accept that humans cannot get rid of this coronavirus with zero confirmed cases. It is time to reset our goal into safe coexistence with the SARS-CoV-2

virus and prepare for the new normal life. The first step of preparation is to accelerate the implementation of vaccination for citizens. Vaccine enhances human immunity and reduces the risk of severe illness and other consequences like death. mRNA vaccines such as BNT162b2 and mRNA-1273 were reported to have more than 90% protective efficacy after 2 doses. On the contrary, the effectiveness of Sputnik V and AZD1222, which are viral vector vaccines, is 91.6% and 76.0%, respectively [2]. Regarding concerns about the reduction in the effectiveness of current vaccines against new variants, a study by Bernal et al. (2021) stated that after 2 doses of BNT162b2 or AZD1222 vaccines, only subtle differences in protective efficacy were observed with the *delta* variant, which is the most common variant in India since April 2021 and recently the omicron variant, compared to *alpha* variant [10]. Therefore, current vaccines are expected to retain their vigorous activity against SARS-CoV-2 variants and partly resolve the fast mutation issue.

On the other hand, repurposing drugs play crucial roles in treating patients with SARS-CoV-2 infection. Casirivimab in combination with Imdevimab, as well as Sotrovimab, which were issued as EUA by the FDA, were also proven to decrease the risk of both COVID19-associated hospital admission and deaths in mild to moderate COVID-19 outpatients. Remdesivir, the only FDA-approved COVID-19 drug, was reported to reduce recovery time from 15 days to 10 days and gave beneficial clinical outcomes to hospitalized patients requiring oxygen support. Their effectiveness remains unchanged against 6 key variants of the SARS-CoV-2 virus [8]. Belonging to the same group with Remdesivir, Nirmatrelvir + Ritonavir (Paxlovid) and Molnupiravir, which recently attracted much attentions due to their promising results in clinical trials, have been expected to be the game changers in this long-term battle [11].

While waiting for a breakthrough in drug development, other alternative options have been proposed for the treatment of COVID-19. These findings usually focused on naturally originated medications since they are safer and more compatible than therapeutic drugs. Mahamud *et al.* suggested the food-originated bioactive peptides drugs, which have been proven to have a better health impact than therapeutic drugs and inhibit chronic disease without side effects [3]. Hossain *et al.* showed that honey could be a possible component against SARS-CoV-2 infection [12]. Another study by Farjana *et al.* used vitamin C against the pathology of COVID-19 due to its crucial role in the immune system [13]. It is also said that *Nigella savita* seed showed promising results in treating and preventing COVID-19 [14]. Other than physical drugs, mental health also played an initial role in preventing this disease, as stated in Hannan et al. [15]. However, the effectiveness of alternatives is still controversial, and need more reports.

While promoting the development of specific COVID-19 drugs, another emerging challenge for treatment also needs overcoming. The increasing demand for medicine, high cost, and the scarcity of drug resources prevent developing countries from accessing qualified drugs and vaccines. This significantly decelerates the new normal status while COVID-19 causes more damage. Transparent and reasonable criteria for COVID-19 drug allocation need to be rapidly established to support more and more countries in the battle against the SARS-CoV-2 virus [16].

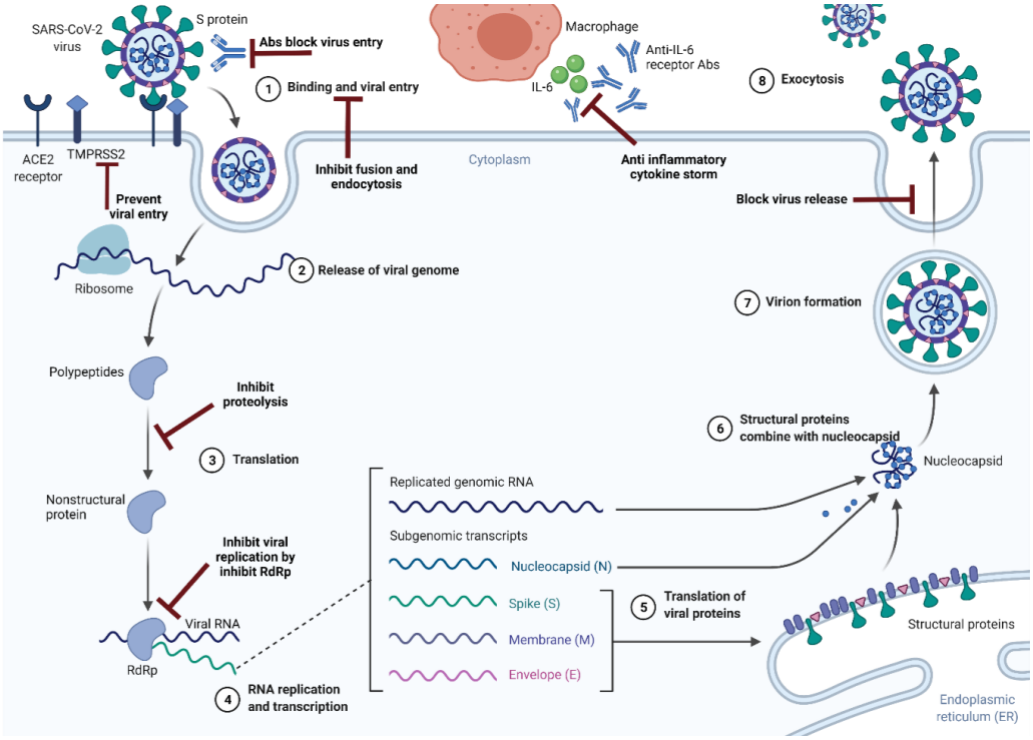

Figure 1. SARS-CoV-2 virus's life circle and drug targets. Antibodies, IL: Interleukin, RNA: ribose nucleotide acid, RdRp: RNA-dependent RNA polymerase. Create with Biorender.com.

CONCLUSION

Besides developing new vaccines against this disease during this public health crisis, it is vital to make progress in the development of specific drugs for COVID-19 treatment to co-exist with the SARS-CoV-2 in the new normal. The current strategy is mostly focused on reproposing drugs with three groups, including antiviral drugs, human antibody products, and immunomodulators. Meanwhile, alternative therapies should be considered.

ACKNOWLEDGEMENT

We also thank Dr. Le Bui Minh (NTT Hi-tech Institute, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam) for the license to use BioRender to create the figures in this work. No external funding supported this work

AUTHOR CONTRIBUTIONS

DTC conceptualized this manuscript. DTC, NLB, YVNT, and SMVN wrote the manuscript. NLB, YVNT, and SMVN prepared the figures and tables. All authors contributed to the revision and approved the final manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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