Antiviral Drugs against COVID-19

Subjects: Critical Care Medicine
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Several FDA-approved available antiviral drugs, alone or in combination, have been screened clinically for their extended use since the early phase of the current pandemic to find a safe and effective treatment option against COVID-19, and many clinical trials of these antiviral drugs are still ongoing. However, an in-depth understanding is required from current clinical literature reports to execute integrated approaches between computational and experimental methods to guarantee high success rates of repositioned drugs. Moreover, multiple challenges associated with repurposed drugs have been identified, including dose adjustments, route of administration, acute/chronic toxicity, appropriate delivery systems, etc..

Keywords: coronavirus disease 2019 (COVID-19) ; repurposing strategy ; repurposed drugs ; remdesivir ; interferon type I ; clinical trials

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has created a lot of burden on the global medical system, public health, and economic and social life of human beings [1][2]. The causative pathogen identified for COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged from viruses of unknown sources [3][4]. SARS-CoV-2 is a type of ß-coronavirus (β-CoV) that belongs to the coronavirus group. The human coronavirus group causes several outbreaks, including the severe acute respiratory syndrome (SARS-CoV) epidemic from 2002 to 2004 and the Middle East respiratory syndrome (MERS-CoV) outbreak in the Middle East, Africa, and South Asia, and many more countries during 2012 [5][6]. Wuhan, China, was the first city for the occurrence of COVID-19, and after that, it spread all over the world, infecting around 218 million people together with over 4.5 million total deaths, according to the COVID-19 global case dashboard of the World Health Organization (WHO), by 29 August 2021 [7]. Based on the data from January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC), which was followed by a pandemic on 11 March 2020 [8].

To date, no effective and approved antiviral treatment is available to fight against COVID-19. However, some recommendations are being practiced concurrently to manage individual patients' needs, such as antipyretic drugs for fever, oxygen therapy for respiratory distresses, antimicrobial therapy with mechanical ventilation applied in some severe cases depending on the clinical condition of the patient, and so on [9][10]. Meanwhile, the drug repurposing strategy is being continuously used in COVID-19 treatment. Drug repurposing or drug repositioning is tactically a rapid process to identify new pharmacological indications rather than the original purpose of investigational, existing, already marketed or FDA-approved drugs for the treatment of diseases. This advantageous method provides a great benefit in circumventing some *de novo* drug design and development stages. Thus, the technique decreases scheduled periods of drug development, reduces failure risk, and protects funds from being wasted [11]. In addition, it is crucial for a drug to be effective, proportionally related to clinical efficacy, or to produce desired pharmacological activities for a specified indication in humans. A potential drug must be passed through efficacy trials to fulfill the principal requirements of clinical efficacy, including several human trial phases [12]. In other words, efficacy trials determine the possibility of an intervention to produce expected results under ideal circumstances or the degree of beneficial effects under real-world clinical settings [13][14].

More importantly, SARS-CoV-2 is the seventh member of the genus β-*coronavirus* and the *Coronavirdiae* family [15]. Genome sequencing of SARS-CoV-2 demonstrated that the virus is almost 79% and 50% identical with the previous two SARS-CoV and MERS coronaviruses, respectively [16]. So, it might be very convenient and rational to repurpose the currently available antiviral drugs used against the two previous viral pandemics (SARS and MERS CoV) or have evidence of previous experience. Furthermore, it has been perceived that drug repurposing has already become a "universal strategy" to face the challenges of the COVID-19 pandemic because of several advantages it offers. These include fewer clinical trial steps, the availability of the formulation and distribution of the existing pharmaceutical supply,

the possibility of more effective treatment of known combination therapy, the discovery of novel mechanisms of actions of old drugs or new classes of medicines, [17] and the elimination of “activation barriers” in the early stages of research, thus ensuring the rapid advancement of any project to disease-oriented research [18].

Several FDA-approved available antiviral drugs, alone or in combination, have been screened clinically for their extended use since the early phase of the current pandemic to find a safe and effective treatment option against COVID-19 [19][20], and many clinical trials of these antiviral drugs are still ongoing. However, an in-depth understanding is required from current clinical literature reports to execute integrated approaches between computational and experimental methods to guarantee high success rates of repositioned drugs. Moreover, multiple challenges associated with repurposed drugs have been identified, including dose adjustments, route of administration, acute/chronic toxicity, appropriate delivery systems, etc. [21][22]. Although many preliminary studies exhibited promising results, several extensive clinical investigations reported contradictory findings with significant adverse effects of these elongated applications of antiviral drugs. However, numerous clinical trials conducted with larger samples/patients have recently disclosed many mixed results, which needs careful study. Therefore, it is essential to review comprehensively the uses of repurposed drugs focusing on the therapeutic strategies, advantages, adverse drug reactions, and respective delivery approaches for instigating an instrumental battle against COVID-19. Likewise, it is also necessary to know the clear disease pathology and critical strategies to identify new drugs capable of protecting against highly contagious viral infections, including the SARS-CoV-2 infection [23]. This article summarizes the current understanding of clinical efficacy and the adverse drug reaction of various antiviral drugs used for SARS-CoV-2-infected patients across the world. Here, we also illustrated **Figure 1** to represent the chemical structures of the seven repurposed antivirals drugs for use against COVID-19.

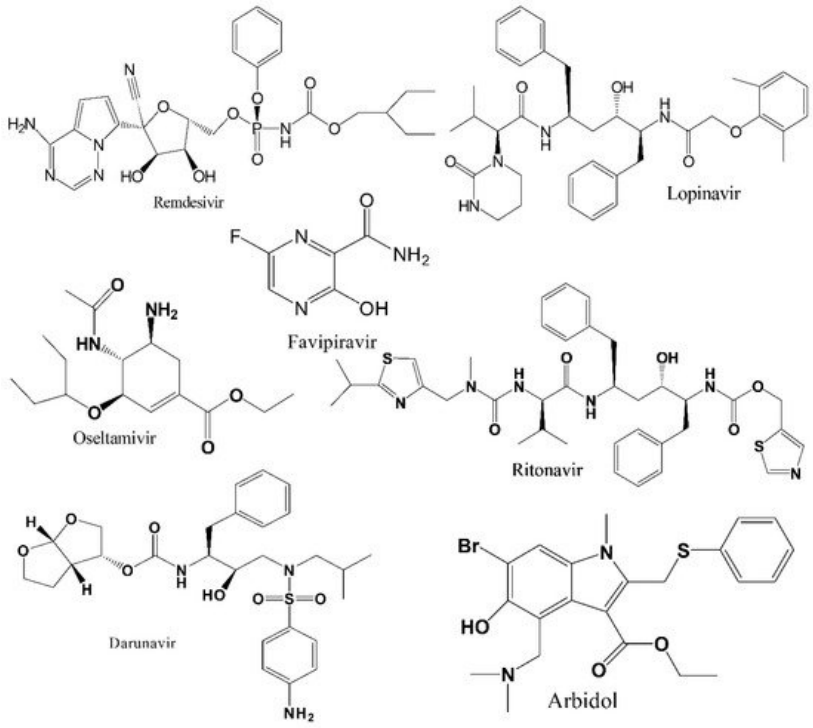

Figure 1. Chemical structures of the selected most promising antiviral drugs against COVID-19.

2. Discussion and Concluding Remarks

The new emergence of such a deadly virus needs potential agents to control it. It can be noted that mass vaccination is not easily affordable in many developing and underdeveloped countries immediately or before 2024 [24]. Additionally, over-populated countries might face some critical situations to ensure vaccines for all people due to vaccine insufficiency, and it might take longer to eradicate the outbreak. Moreover, the delta variant of concern has shown to be several times more resistant against vaccine-induced immunity [25]. This crucial situation calls for effective treatment tools/antiviral agents to fight against the deadly infectious disease. This review mainly focuses on the efficiency and adverse effects of repurposing antiviral drugs potentially used to treat COVID-19.

Various drugs are being used as repurposing drugs, as there is no drug or effective treatment strategy against COVID-19. Therefore, the most promising seven antiviral drugs were taken under consideration to evaluate their efficacy and also their adverse effects in various levels of COVID-19 patients.

The very first drug and most widely used one was RDV. Though several studies mentioned above showed reduced mortality, shorter hospital stay, and better improvement of symptoms, several studies have been reported it to be insignificant in the case of COVID-19 patients' recovery. Notably, the Macaque experiment stated that RDV was only efficient in viral clearance from the lower respiratory tract, not the upper one [26]. Another randomized controlled study conducted by Wang et al. [27] suggested no efficacy of RDV on the respiratory tract, neither upper nor lower. We can conclude by evaluating the above data that RDV might be effective for severe patients in mitigating the fatality rate and improvement of clinical conditions. The WHO has recommended RDV against in non-severe patients, which might match with the current findings.

FPV has shown great efficacy in this crucial situation, yet it is not patient-friendly due to its high dose. The studies discussed above revealed that FPV is a potential cure for COVID-19, both in severe and mild cases. Chen et al. [28] reported a positive effect of FPV compared to ARB, as the former showed better improvement of symptoms like cough, pyrexia, and difficulty breathing. The drug is beneficial in alleviating symptoms, reducing viral load and hospital stay, but still, it is considered risky due to severe side effects like teratogenicity and embryotoxicity [29]. This drug was very effective against H1N1 virus, which is also an RNA virus and has shown potential antiviral effects, perhaps most efficient in viral clearance. There has been no toxicity detected for its huge loading dose, but some adverse effects have been reported; cardiovascular complications, nausea, vomiting, diarrhea, and kidney injuries are the common ones. Several studies also compared the efficacy among FPV, hydroxychloroquine, chloroquine, and IFN, which had minimal significant difference. LPV/RTV combination was also a drug of choice for COVID-19 in the early stages of the pandemic. However, this combination proved to be insignificant in most of the cases studied, with some exceptions. The combination rather became the reason behind serious complications like diarrhea, gastrointestinal disturbance, electrolyte imbalance, and severe acute kidney injury in patients with both severe and mild COVID-19.

INF therapy is one of the promising treatments for COVID-19 now. Several subcategories of INF are known, such as IFN-alpha 1a, IFN-alpha 1b, IFN-beta 1a, IFN-beta 1b, IFN-gamma, and IFN-lambda. All have shown a variety of efficacy without severe side effects. They have worked to the betterment of patients' condition and reduced the fatality rate among severe patients. Several studies were also carried out to evaluate and compare the potentials of these variants. Recombinant IFN has proven to be more potent than traditional ones. An efficient therapy known as triple therapy is a combination of IFN/LPV/r/RBV that has shown amazing results. Type I interferons (IFN-I, IFN-α, and IFN-ß) are immunomodulatory drugs that can induce antiviral effects and may induce pro-inflammatory activity, which has turned out to be beneficial for early treatment of COVID-19 [30]. Combination with other antiviral agents may mitigate the adverse effects as well as improve the clinical condition of the patients.

ARB has shown noteworthy effects in alleviating symptoms of COVID-19 and shortening the time for converting the PCR result from positive to negative. The potential antiviral agent works well both alone and in combination with various other agents like HCQ, RBV, and IFN. Antibiotic therapy alongside ARB is just the icing on the cake, showing prompt activity in quick recovery and reduction of fatality rate. It has proved to be more efficacious than other drugs like LPV/RTV and HCQ. All these have made it a potential agent in this pandemic situation. We can add oseltamivir to this list, but the drug showed great positive effects in severe patients when used early. Darunavir is emerging as a potent antiviral drug by lowering the mortality rate and hospital stay, but more studies are required to extensively verify its safety profile.

HCQ, LPV/RTV, and many other drugs, which were thought to be a treatment option earlier, are already banned by the WHO. FPV, ARB, and oseltamivir are in the pool of acceptable drugs for COVID-19, but there are still many randomized trials going on to assess their safety profiles. RDV is recommended in severe conditions considering its adverse effects that require limited use of the drug. Boosting the immune system is believed to be beneficial, so IFN type I might exert immunomodulation through its antiviral effects by stimulating interferon-stimulated gene (ISG).

As patients with COVID-19 might face multiple pathological dysfunctions, they must be prescribed multi-drug therapies [31]. Moreover, several pieces of evidence have demonstrated that combination therapy is superior to monotherapy, as the multiple drugs might heal by acting on multiple receptors [32]. Particularly, combination therapy in COVID-19 has become an excellent choice to wrestle against the disease. Several diagnoses revealed that secondary infections have become of paramount importance as an after-effect of COVID-19, and have some saddening consequences. A combination of potential antivirals with antibiotics is used to fight the secondary infections produced due to lessened immunity, along with the viral infection [33]. Interferon uses an immunomodulator that has served well for COVID-19, and its combination with antiviral agents gives the best results. Moreover, the combination lowers the time taken to reduce viral shedding significantly [34]. The mechanism could be the dual action of antivirals and immunomodulatory agents; one weakens the virus, and the latter strengthens the immunity so the body can recover faster, through confirmation or justification of this

mechanism is yet to be provided. However, to define the exact mechanism and efficacy profile of the stated combinations in the current review, more precise investigation with larger data and evidence might be required.

References

1. Ashraf, B.N. Economic impact of government interventions during the COVID-19 pandemic: International evidence from financial markets. J. Behav. Exp. Financ. 2020, 27, 100371.
2. Hossain, M.J.; Ahmmed, F.; Rahman, S.; Sanam, S.; Emran, T.B.; Mitra, S. Impact of online education on fear of academic delay and psychological distress among university students following one year of COVID-19 outbreak in Bangladesh. Heliyon 2021, 7, e07388.
3. Gollakner, R.; Capua, I. Is COVID-19 the first pandemic that evolves into a panzootic? Vet. Ital. 2020, 56, 11–12.
4. Yoo, H.S.; Yoo, D. COVID-19 and veterinarians for one health, zoonotic- and reverse-zoonotic transmissions. J. Vet. Sci. 2020, 21, e51.
5. Gupta, N.; Singhai, M.; Garg, S.; Shah, D.; Sood, V.; Singh, S.K. The missing pieces in the jigsaw and need for cohesive research amidst coronavirus infectious disease 2019 global response. Med. J. Armed Forces India 2020, 76, 132–135.
6. Decaro, N.; Lorusso, A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. Vet. Microbiol. 2020, 244, 108693.
7. World Health Organization. Weekly Operational Update on COVID-19—20 July 2021; World Health Organization: Geneva, Switzerland, 2021; pp. 1–13.
8. Hossain, M.J.; Kuddus, M.R.; Rahman, S.M.A. Knowledge, attitudes, and behavioral responses toward COVID-19 during early phase in bangladesh: A questionnaire-based study. Asia Pac. J. Public Health 2021, 33, 141–144.
9. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Available online: https://stacks.cdc.gov/view/cdc/88624 (accessed on 30 August 2021).
10. Hossain, M.J. Is Bangladesh moving toward herd immunity? Current COVID-19 perspective. Bangladesh J. Infect. Dis. 2020, 7 (Suppl. S2), S63–S66.
11. Pushpakom, S.; Iorio, F.; Eyers, P.A.; Escott, K.J.; Hopper, S.; Wells, A.; Doig, A.; Guilliams, T.; Latimer, J.; McNamee, C.; et al. Drug repurposing: Progress, challenges and recommendations. Nat. Rev. Drug Discov. 2019, 18, 41–58.
12. Hossain, M.J.; Kuddus, M.R.; Rashid, M.A.; Sultan, M.Z. Understanding and dealing the SARS-CoV-2 infection: An updated concise review. Bangladesh Pharm. J. 2021, 24, 61–75.
13. Godwin, M.; Ruhland, L.; Casson, I.; MacDonald, S.; Delva, D.; Birtwhistle, R.; Lam, M.; Seguin, R. Pragmatic controlled clinical trials in primary care: The struggle between external and internal validity. BMC Med. Res. Methodol. 2003, 3, 28.
14. Viveiros Rosa, S.G.; Santos, W.C. Clinical trials on drug repositioning for COVID-19 treatment. Rev. Panam. Salud Publica Pan Am. J. Public Health 2020, 44, e40.
15. Wrapp, D.; Wang, N.; Corbett, K.S.; Goldsmith, J.A.; Hsieh, C.L.; Abiona, O.; Graham, B.S.; McLellan, J.S. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020, 367, 1260–1263.
16. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020, 395, 565–574.
17. Oprea, T.I.; Bauman, J.E.; Bologa, C.G.; Buranda, T.; Chigaev, A.; Edwards, B.S.; Jarvik, J.W.; Gresham, H.D.; Haynes, M.K.; Hjelle, B.; et al. Drug repurposing from an academic perspective. Drug Discov. Today Ther. Strateg. 2011, 8, 61–69.
18. Senanayake, S.L. Drug repurposing strategies for COVID-19. Future Drug Discov. 2020, 2, FDD40.
19. Young, B.E.; Ong, S.W.X.; Kalimuddin, S.; Low, J.G.; Tan, S.Y.; Loh, J.; Ng, O.-T.; Marimuthu, K.; Ang, L.W.; Mak, T.M.; et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020, 323, 1488–1494.
20. Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir. Med. 2020, 8, 475–481.

21. Parvathaneni, V.; Gupta, V. Utilizing drug repurposing against COVID-19—Efficacy, limitations, and challenges. Life Sci. 2020, 259, 118275.
22. Marra, F.; Smolders, E.J.; El-Sherif, O.; Boyle, A.; Davidson, K.; Sommerville, A.J.; Marzolini, C.; Siccardi, M.; Burger, D.; Gibbons, S.; et al. Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. Drugs R&D 2021, 21, 9–27.
23. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.L. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 2021, 19, 141–154.
24. OECD. Policy Responses to Coronavirus (COVID-19). Coronavirus (COVID-19) Vaccines for Developing Countries: An Equal Shot at Recovery. Available online: https://www.oecd.org/coronavirus/policy-responses/coronavirus-covid-19-vaccines-for-developing-countries-an-equal-shot-at-recovery-6b0771e6/ (accessed on 27 July 2021).
25. Bari, M.S.; Hossain, M.J.; Akhter, S.; Emran, T.B. Delta variant and black fungal invasion: A bidirectional assault might worsen the massive second/third stream of COVID-19 outbreak in South-Asia. Ethics Med. Public Health 2021, 19, 100722.
26. Williamson, B.N.; Feldmann, F.; Schwarz, B.; Meade-White, K.; Porter, D.P.; Schulz, J.; Van Doremalen, N.; Leighton, I.; Yinda, C.K.; Pérez-Pérez, L.; et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 2020, 585, 273–276.
27. Wang, Y.; Zhang, D.; Du, G.; Du, R.; Zhao, J.; Jin, Y.; Fu, S.; Gao, L.; Cheng, Z.; Lu, Q.; et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020, 395, 1569–1578.
28. Chen, C.; Zhang, Y.; Huang, J.; Yin, P.; Cheng, Z.; Wu, J.; Chen, S.; Zhang, Y.; Chen, B.; Lu, M.; et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv 2020.
29. Nagata, T.; Lefor, A.K.; Hasegawa, M.; Ishii, M. Favipiravir: A new medication for the Ebola virus disease pandemic. Dis. Med. Public Health Prep. 2015, 9, 79–81.
30. Sharun, K.; Tiwari, R.; Dhama, K.; Emran, T.B.; Rabban, A.A.; Al Mutair, A. Emerging SARS-CoV-2 variants: Impact on vaccine efficacy and neutralizing antibodies. Hum. Vaccines Immunother. 2021, 17, 1–4.
31. Hossain, M.J. Impact of COVID-19 pandemic among health care providers in Bangladesh: A systematic review. Bangladesh J. Infect. Dis. 2020, 7 (Suppl. S2), S8–S15.
32. Hossain, M.J.; Islam, M.S.; Shahriar, S.; Sanam, S.; Emran, T.B.; Khatun, C.S.; Islam, M.R.; Mitra, S.; Dhama, K. Comedication of rabeprazole sodium causes potential drug-drug interaction with diabetic drug linagliptin: In-vitro and in-silico approaches. J. Exp. Biol. Agric. Sci. 2021, 9, 528–542.
33. Lai, C.C.; Wang, C.Y.; Hsueh, P.R. Coinfections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? J. Microbiol. Immunol. Infect. 2020, 53, 505–512.
34. Zuo, Y.; Liu, Y.; Zhong, Q.; Zhang, K.; Xu, Y.; Wang, Z. Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: A retrospective study in two designated hospitals in Anhui, China. J. Med. Virol. 2020, 92, 2666–2674.