

REVIEW ARTICLE

Repurposing of Antiviral Drugs for Covid-19 Therapy

Hussain Mustatab Wahedi, Deeba Amraiz

ABSTRACT

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) is one of the biggest health challenges across the globe ever since its eruption in late 2019. Novelty, contagiousness, and lethality of the virus demand the expedited production of potential therapeutic agents and strategies against it. Since no COVID-19 specific drug is available yet, it persists a crucial challenge to determine what therapeutic strategies should be adopted for the treatment of coronavirus patients. Until there is any specific drug for COVID-19, repurposing of the existing FDA-approved drugs is the most suitable approach to treat the severely ill patients of COVID-19. This review will summarize the existing antiviral drugs being repurposed and probed for their potential as effective anti-COVID-19 drugs all over the world.

Key Words: *Antiviral Drugs, Coronavirus, Drug Repurposing, Drug Repositioning.*

How to cite this: Wahedi HM, Amraiz D. Repurposing of Antiviral Drugs for Covid-19 Therapy. *Life and Science*. 2020; 1(suppl): 22-31. doi: <http://doi.org/10.37185/LnS.1.1.151>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited

Introduction

The present pandemic caused by SARS-CoV-2 has shown unprecedented challenges to the global health system.^{1,2} SARS-CoV-2 like other coronaviruses is known to induce abnormal, inadequate host immune response linked with a severe respiratory lung disorder. It can also lead to multi-organ failure.³ The World Health Organization (WHO) proclaimed it as a pandemic on 11th March 2020.⁴ The outbreak has spread around the globe with 18, 793, 522 confirmed cases of coronavirus including 707, 715 mortalities as of 6th August 2020.⁵ Nearly 220 countries have reported the confirmed cases of coronavirus in all continents except Antarctica.⁶ Pakistan is also one of the countries which are affected by this pandemic. Pakistan has reported 282,645 confirmed cases including 6,052 deaths as of 7th August 2020.⁷ There is a dire need to develop an effective therapeutic strategy against COVID-19 as the number of deaths and as well as confirmed cases are still growing. This review takes

into account the antiviral drugs along with their mechanisms of action that are in clinical trials as potential anti-COVID-19 drugs. The review summarizes the details of phases and country-wise distribution of the clinical trials underway on repurposed antiviral drugs (Table 1).

Fusion Inhibitors

Umifenovir

Umifenovir (Arbidol) is a fusion inhibitor drug clinically approved to treat Influenza. Arbidol halts the viral fusion with the cell membrane as well as with the endosome by incorporation into the membrane. Arbidol also intrudes with the hydrogen bonding meshwork of phospholipids.⁸ Deng et al., (2020) have demonstrated that compared with lopinavir-ritonavir (LPV/r) alone, the combined treatment of arbidol and LPV/r has exhibited more profound results in COVID-19 patients.⁹ Chen et al., (2020a) has reported the findings of a randomized clinical trial which showed an increased recovery rate in the arbidol group as compared with favipiravir.¹⁰ Another randomized phase IV clinical trial was initiated in January 2020 to evaluate the efficacy of arbidol versus standard of care treatment (NCT04260594). Chen et al., (2020c) highlighted the role of arbidol in combination with adjuvant therapy in shortening the recovery time and fever of the SARS-CoV-2 patients.¹¹ A phase IV clinical trial to investigate the therapeutic potential of LPV/r and

Department of Biological Sciences

National University of Medical Sciences, Rawalpindi

Correspondence:

Dr. Hussain Mustatab Wahedi

Assistant Professor, Biological Sciences

National University of Medical Sciences, Rawalpindi

E-mail: hmwahedi@gmail.com

Funding Source: NIL; Conflict of Interest: NIL

Received: Aug 31, 2020; Revised: Sep 23, 2020

Accepted: Nov 01, 2020

Table 1: List of antiviral drugs under clinical trials with details of trial phases and country/countries the trials are being conducted in

Drug	Original Indication	Mechanism of Action	Trial Identifier	Phase	Country
Arbidol	Influenza	Fusion Inhibitor	NCT04260594	4	China
			NCT04252885	4	China
			ChiCTR2000029621	4	China
			IRCT20200322046833N1	3	Iran
			IRCT20180725040596N2	3	Iran
			NCT04350684	4	Iran
			IRCT20080901001165N46	3	Iran
			IRCT20200523047550N1	3	Iran
			IRCT20151227025726N15	4	Iran
Remdesivir	Ebola Virus/ Broad Spectrum	Viral Polymerase Inhibitor	EUCTR2020-001366-11-ES	N/A	Spain
			NCT04257656	3	China
			ISRCTN83971151	3	Saudi Arabia; Indonesia; Iran; Ireland; Israel; Italy; Kenya; Malaysia; Norway; Peru; Philippines; Qatar; South Africa; Spain; Switzerland; Thailand; Argentina; Brazil; Canada; Germany; Lebanon Honduras; India
			NCT04280705	3	United States; United Kingdom; Denmark; Japan Germany; Greece; Korea, Republic of Mexico; Singapore; Spain;
			JPRN-jRCT2031190264	3	United States; Korea; Japan
			EUCTR2020-001366-11-IE	N/A	Portugal; France; Canada; Spain; Ireland; Australia; Norway; Italy; India
			NCT04292730	3	Sweden; United States; China France; Germany; Hong Kong; Italy; Japan; Korea; Republic of Netherlands; Singapore; Spain; Switzerland; Taiwan; United Kingdom; Iran
			NCT04315948	3	France; Luxembourg
			NCT04401579	3	United States; Japan; Korea, Republic of Mexico; Singapore
			NCT04409262	3	United States
			NCT04431453	2/3	United States and United Kingdom
			EUCTR2020-001803-17-GB	2/3	United States; Italy; United Kingdom; Spain
Favipiravir	Influenza/ Broad spectrum	Viral Polymerase Inhibitor	ChiCTR2000029548	N/A	China
			ChiCTR2000030894	4	China
			ChiCTR2000030987	2/3	China

			NCT04319900	2/3	China
			NCT04336904	3	Italy
			JPRN-JapicCTI-205238	3	Japan
			JPRN-jRCTs031190226	2	Japan
			NCT04349241	3	Egypt
			NCT04351295	2/3	Egypt
			NCT04358549	2	United States
			EUCTR2020-001449-38-GB	3	United Kingdom
			NCT04373733	3	United Kingdom
			IRCT20151227025726N14	3	Iran
			IRCT20150808023559N20	2	Iran
			IRCT20200428047228N1	3	Iran
			JPRN-jRCTs031200026	3	Japan
			JPRN-jRCTs041190120	2	Japan
			TCTR20200514001	2/3	Thailand
			CTRI/2020/05/025114	3	India
			NCT04346628	2	United States
			NCT04402203	2/3	Bangladesh
			EUCTR2020-001904-41-GB	2	United Kingdom
			NCT04411433	3	Turkey
			ChiCTR2000029996	2	China
			NCT04434248	2/3	Russian Federation
			NCT04425460	3	China; Germany; Romania
			CTRI/2020/06/025799	3	India
			CTRI/2020/06/025957	3	India
			JPRN-jRCTs041200025	2	Japan
			IRCT20150107020592N26	3	Iran
			EUCTR2020-002106-68-GB	2	United Kingdom
			NCT04464408	2/3	N/A
Oseltamivir	Influenza	Viral Neuraminidase Inhibitor	NCT04255017	4	China
			NCT04303299	3	Thailand
			IRCT20200410047009N1	4	Iran
			NCT04338698	3	Pakistan
			NCT04261270	3	China
Ribavirin	HCV	Viral Polymerase Inhibitor	NCT04494399	2	Hong Kong
			NCT04392427	3	Egypt
			NCT04356677	1	United States
Azvadine	HBV, HCV, HIV	Reverse Transcriptase Inhibitor	ChiCTR2000029853	N/A	China
			ChiCTR2000030424	N/A	China
			ChiCTR2000030487	N/A	China
			ChiCTR2000030041	N/A	China

			ChiCTR2000032769	N/A	China
			NCT04425772	N/A	N/A
Clevudine	HBV	Viral Polymerase Inhibitor	NCT04347915	2	Republic of Korea
Sofosbuvir	HCV	Viral Polymerase Inhibitor	DRKS00022203	N/A	Egypt
			CTRI/2020/06/025760	N/A	India
			IRCT20200624047908N1	3	Iran
			IRCT20200328046886N1	3	Iran
			IRCT20200128046294N2	3	Iran
			NCT04460443	2/3	Egypt
			IRCT20200324046850N2	2	Iran
			NCT04468087	2/3	Brazil
			IRCT20100228003449N29	2/3	Iran
Emtricitabine/Tenofovir	HIV-1	Reverse Transcriptase Inhibitor	ChiCTR2000029468	N/A	China
			NCT04405271	3	Argentina
			NCT04334928	3	Spain
			EUCTR2020-001385-11-ES	3	Spain
Lopinavir /Ritonavir	HIV-1	Viral Protease Inhibitor	ChiCTR2000029741	4	China
			EUCTR2020-000936-23-FR	3	United Kingdom; France; Belgium; Germany; Luxembourg; Netherlands; Spain
			EUCTR2020-001188-96-FR	3	France
			NCT04328012	2/3	United States
			EUCTR2020-001448-24-GB	3	Ghana; United Kingdom; Nigeria; South Africa; India
			JPRN-jRCTs031190227	2	Japan
			NCT04351724	2/3	Austria
			NCT04359095	2/3	Colombia
			NCT04365582	3	France
			IRCT20190804044429N1	2/3	Iran
			IRCT20200418047116N1	2	Iran
			LBCTR2020043495	3	Lebanon
			PACTR202004893013257	3	Ghana
			IRCT20200517047485N1	3	Iran
			EUCTR2020-001528-32-IT	3	Italy
			EUCTR2020-001549-38-DE	3	Germany
			NCT04455958	2	United States
			PACTR202006537901307	3	Burkina Faso; Cameroon; Democratic Republic of the Congo; Equatorial Guinea; Ethiopia; Ethiopia; Uganda; Ghana; Guinea; Cote Divoire; Kenya; Mozambique; Sudan; Tanzania;
Darunavir	HIV	Viral Protease Inhibitor	NCT04435587	4	Thailand
Atazanavir	HIV	Viral Protease Inhibitor	IRCT20200504047298N1	3	Iran
			NCT04452565	2/3	United States
			IRCT20100228003449N30	2/3	Iran
Nelfinavir	HIV	Viral Protease Inhibitor	jRCT2071200023	N/A	Japan
Nitazoxanide	Diarrhea		NCT04423861	2	Brazil

Viral Nucleoprotein Inhibitor	NCT04441398	2/3	Brazil
	NCT04343248	3	United States
	NCT04359680	3	United States
	NCT04406246	4	Mexico
	NCT04435314	2	Brazil
	CTRI/2020/06/025849	2	India
	NCT04486313	3	United States
	NCT04459286	2	Nigeria
	NCT04463264	2/3	Argentina

arbidol against COVID-19, completed in May 2020 (NCT04252885) showed that the treatment with LPV/r or arbidol has few effects in improving the clinical results of patients.¹² Moreover, Zhu et al., (2020) demonstrated that umifenovir treatment is better to LPV/r in COVID-19.¹³ Different phase III and phase IV clinical trials with arbidol are underway in China (ChiCTR2000029621) and Iran (IRCT20200322046833N1, IRCT20180725040596N2, NCT04350684, IRCT20080901001165N46, IRCT20200523047550N1, IRCT20151227025726N15).

Viral Polymerase Inhibitors

Remdesivir

Remdesivir is an antiviral agent with an ability of inhibitory activity against RNA viruses.¹⁴ Remdesivir is a nucleotide analog that decreases the viral RNA production by obscuring viral RNA polymerase. Its antiviral mechanism is delayed chain termination of nascent viral RNA.¹⁵ Holshue et al., (2020) showed that intravenous administration of the antiviral drug remdesivir has good therapeutic results in a COVID-19 patient in the USA.¹⁶ To analyze the curative potential of remdesivir against COVID-19, a phase III clinical trial was conducted on 237 SARS-CoV-2 hospitalized patients in China (NCT04257656). The outcomes exhibited that remdesivir was linked with non-significant faster clinical recovery among patients. However, there was an early halt of drug administration in 12% of participants due to the ill effects on the gastrointestinal tract, liver, and cardiopulmonary status.¹⁷ Later in February 2020, another adaptive, randomized, phase III clinical trial was conducted in the USA. In this trial 1062 patients were enrolled, the patients in the experimental group were administered with the first dose of 200 mg of remdesivir followed by the 100mg up to ten

days (NCT04280705). The results of this study showed that remdesivir significantly reduced respiratory tract infection and recovery time in coronavirus patients.¹⁸ In addition to these, another randomized phase III trial was conducted with 4891 participants in the USA (NCT04292899). The study was intended to investigate the effectiveness and safety of two remdesivir regimens (5 days and 10 days of treatment). However, the results showed no appreciable difference between the two arms.¹⁹ National Institute of Allergy and Infectious Diseases (NIAD) initiated a multicenter, phase III clinical trial to compare the antiviral potential of remdesivir with the combination of remdesivir and baricitinib (NCT0441579). In another phase III clinical trial, 1113 participants were recruited to analyze the efficacy of two remdesivir regimens (NCT04292730). Many other phase III clinical trials with the viral polymerase inhibitor, remdesivir in coronavirus patients have been started in France and Luxembourg (NCT04315948), United States (NCT04409262), Germany, Argentina, Brazil, Canada, Spain, Honduras, Indonesia, Iran, Ireland, Israel, Italy, India, Kenya, Norway, Peru, Philippines, Malaysia Saudi Arabia, South Africa, Qatar, Switzerland, Lebanon, Thailand (ISRCTN83971151), USA, Korea, Japan (JPRN-jRCT2031190264), Portugal, France, Canada, Spain, Ireland, Australia, Norway, Italy, India (EUCTR2020-001366-11-IE), United States and United Kingdom (NCT04431453), USA, Spain, Italy, UK (EUCTR2020-001803-17-GB) and Spain (EUCTR2020-001366-11-ES).

Favipiravir

Favipiravir (Avigan) is an antiviral agent with the potential to inhibit viral RNA polymerase.²⁰ Favipiravir exhibits its antiviral activity by targeting the RNA polymerase (catalytic domain), halting the addition of nucleotides at the time of viral RNA

replication. The misregulation in RNA replication of the virus produces higher transition mutations which prompts destructive mutagenesis.²⁰ It has been employed for the treatment of various ailments including Influenza and Ebola.²¹ Current *in-vitro* and clinical studies have reassigned favipiravir as a prospective candidate drug for the COVID-19 treatment. Clinical trials with favipiravir against SARS-CoV-2 have been carried out strenuously in many countries of the world. Clinical trial initiated in February 2020 in China to investigate the therapeutic potential of favipiravir in combination with baloxavir marboxil, in coronavirus patients (ChiCTR2000029544) showed no promising results.²² However, Chen et al., (2020) has reported that coronavirus patients administered with favipiravir showed an increased recovery rate (71.43%) as compared to arbidol (55.86%). The period of cough and fever was also appreciably reduced in the favipiravir treated group than in the arbidol group.¹⁰ Another phase III clinical trial is in process since March 2020 in China to compare the therapeutic potential of favipiravir with combination of favipiravir and chloroquine phosphate (NCT04319900). A phase IV multicenter trial in China evaluating the efficacy of favipiravir in conjugation with tocilizumab (ChiCTR2000030894).and various phase II and phase III clinical trials are commenced to investigate the effectiveness of favipiravir against SARS-CoV-2 in China (ChiCTR2000030987, ChiCTR2000029996), Italy (NCT04336904), Japan (JPRN-JapicCTI-205238, JPRN-jRCTs031190226, JPRN-jRCTs031200026, JPRN-jRCTs041200025, JPRN-jRCTs041190120, Bangladesh (NCT04402203), Thailand (TCTR20200514001), United Kingdom (EUCTR2020-001904-41-GB, EUCTR2020-002106-68-GB, NCT04373733, EUCTR2020-001449-38-GB), Turkey (NCT04411433), India (CTRI/2020/06/025799, CTRI/2020/06/025957, CTRI/2020/05/025114), China, Germany, Romania (NCT04425460), Iran (IRCT20151227025726N14, IRCT20150808023559N20, IRCT20200428047228N1, IRCT20150107020592N26), Saudi Arabia (NCT04464408), Russian Federation (NCT04434248), United States (NCT04346628, NCT04358549), Egypt (NCT04349241, NCT04351295).

Sofosbuvir

Sofosbuvir is a nucleotide analog, with antiviral activity against the hepatitis C virus (HCV). Sofosbuvir is a well-known inhibitor of NS5B polymerase of HCV. Sofosbuvir is recommended in combination with daclatasvir, ledipasvir, velpatasvir, or peginterferon-alfa.²³ Recently, a phase II, phase III clinical trial of sofosbuvir was initiated on 1st August 2020 in Egypt to evaluate the efficacy of sofosbuvir with or without ribavirin against SARS-CoV-2 (NCT04460443). Different clinical trials have been initiated with sofosbuvir in India (CTRI/2020/06/025760) and with a combination of sofosbuvir and daclatasvir in Egypt (DRKS00022203), Iran (IRCT20200624047908N1, IRCT20200128046294N2), and Brazil (NCT04468087). Sofosbuvir is also in clinical trials, in combination with ribavirin (IRCT20200328046886N1), ritonavir (IRCT20200324046850N2), and ledipasvir (IRCT20100228003449N29) in Iran.

Ribavirin

Ribavirin is an antiviral drug use for the treatment of hepatitis C. Ribavirin exhibits its antiviral activity by inhibition of viral RNA polymerase. and inosinate dehydrogenase (IMP dehydrogenase) which is essential for the production of guanosine triphosphate, ultimately causing destructive mutagenesis.²⁴ Hung et al., (2020) demonstrated in a phase II clinical trial that triple combination antiviral drug therapy ribavirin, LPV/r, and interferon beta-1b was safe and superior in shortening the recovery time and reducing the viral load of COVID-19 patients.²⁵ Another phase II clinical trial to analyze the effectiveness of ribavirin and interferon beta-1b against SARS-COV-2 (NCT04494399) is underway since July in Hong Kong. The combination of ribavirin with LPV/r or interferon beta-1b is recommended by the China National Practice Guidelines for the treatment of COVID-19 patients.²⁶ Currently, different clinical trials are analyzing the therapeutic potential of ribavirin alone or in combination with nitazoxanide and ivermectin in the USA (NCT04356677) and Egypt (NCT04392427) respectively.

Clevudine

Clevudine is an antiviral drug clinically approved in Korea and the Philippines for the treatment of

hepatitis B. Clevudine is a nucleoside analog, involved in the inhibition of hepatitis B virus (HBV) polymerase by clevudine 5' triphosphate.²⁷ A phase II clinical trial has been initiated on 6th May 2020 in Korea to analyze the safety and efficacy of 120 mg dose of clevudine versus placebo once-daily administration for 14 days in patients suffering from COVID-19 (NCT04347915).

Viral Neuraminidase Inhibitors

Oseltamivir

Oseltamivir (Tamiflu) is an antiviral drug clinically approved for the treatment of Influenza. It targets the viral neuraminidase to inhibit the release of viral particles from host cells, consequently decreasing the proliferation of the influenza virus in the respiratory tract.²⁸ A study in China reported that treatment with oseltamivir has shown no positive clinical outcome in hospitalized patients of coronavirus.²⁹ A randomized phase IV clinical trial was initiated on 1st February 2020 in China to investigate the efficacy of three antiviral drugs, arbidol hydrochloride, lopinavir-ritonavir, and oseltamivir against SARS-CoV-2 pneumonia (NCT04255017). A phase III randomized clinical trial was initiated in Thailand to analyze the different combinations of oseltamivir, chloroquine, and favipiravir as a therapeutic strategy to combat the ill effects of COVID-19 (NCT04303299). Various clinical trials are in progress to analyze the curative potential of oseltamivir in treating COVID-19 in various combinations, such as with naproxen in Iran (IRCT20200410047009N1), with ASC09F and ritonavir in China (NCT04261270). In Pakistan oseltamivir is in a clinical trial in combination with hydroxychloroquine and azithromycin (NCT04338698).³⁰

Reverse Transcriptase Inhibitors

Azvadine

Azvadine is an inhibitor of reverse transcriptase with antiviral potential against HBV, HCV, and human immunodeficiency virus (HIV).³¹ Ren et al., (2020) reported that azvadine has effectively reduced the recovery time in the treatment of SARS-CoV-2, however, clinical trials of azvadine treating SARS-CoV-2 with a large sample size are warranted.³² Moreover, in June 2020 another clinical trial has been initiated with azvadine for the treatment of coronavirus patients (NCT04425772). Different

clinical trials are ongoing with azvadine to evaluate its antiviral potential against SARS-CoV-2 in China (ChiCTR2000029853, ChiCTR2000030424, ChiCTR2000030487, ChiCTR2000030041, ChiCTR2000032769).

Emtricitabine/Tenofovir

Emtricitabine/Tenofovir (Truvada), is a combination nucleoside reverse transcriptase inhibitor used to treat or prevent HIV-1.³³ A randomized clinical trial was initiated in China as a therapeutic regimen for coronavirus patients with lopinavir-ritonavir and emtricitabine/tenofovir (ChiCTR2000029468). Different clinical trials are ongoing with emtricitabine/tenofovir for the prevention of COVID-19 in Argentina (NCT04405271) and Spain (NCT04334928, EUCTR2020-001385-11-ES).

Viral Protease Inhibitors

Lopinavir-Ritonavir

Lopinavir is an HIV-1 specific protease inhibitor. Lopinavir is administered in combination with ritonavir as its bioavailability through oral route is very low. The co-administration of lopinavir with ritonavir also improves its antiviral activity. The mechanism of action of lopinavir is to mimic the peptide linkage usually targeted by the viral protease, thus inhibiting the activity of the HIV-1 protease.³⁴ Cao et al., (2020) have reported no significant clinical outcome in lopinavir-ritonavir arm of a clinical trial in hospitalized coronavirus patients compared to standard care.³⁵ However, a study from South Korea has reported that viral protease inhibitor (LPV/r) treatment has reduced SARS-CoV-2 titers with no or very little viral load detected in the follow-up study.³⁶ Another randomized, multicenter phase IV trial was initiated in China to compare the efficacy of chloroquine phosphate and lopinavir-ritonavir (ChiCTR2000029741). Different phase II and Phase III clinical trials with LPV/r in coronavirus patients are ongoing in Spain, Belgium, France, Germany, Netherlands, United Kingdom, Luxembourg (EUCTR2020-000936-23-FR), France (EUCTR2020-001188-96-FR, NCT04365582), USA (NCT04328012, NCT04455958), Ghana, Nigeria, South Africa, United Kingdom, India (EUCTR2020-001448-24-GB), Japan (JPRN-jRCTs031190227), Austria (NCT04351724), Colombia (NCT04359095), Iran (IRCT20190804044429N1, IRCT20200418047116N1,

(IRCT20200517047485N1), Lebanon (LBCTR2020043495), Ghana (PACTR202004893013257), Italy (EUCTR2020-001528-32-IT), Germany (EUCTR2020-001549-38-DE), Democratic Republic of the Congo, Burkina Faso, Cameroon, Equatorial Guinea, Cote Divoire, Ethiopia, Ghana, Kenya, Tanzania, Mozambique, Sudan, and Uganda (PACTR202006537901307).

Darunavir

Darunavir is a second-generation approved protease inhibitor for the treatment of HIV.³⁷ Chen et al., (2020) reported the results of clinical trials showing that darunavir/cobicistat failed to increase the nucleic acid negative conversion rate in comparison to the control group for COVID-19 patients.³⁸ Another phase IV clinical trial has been initiated in Thailand to compare the efficacy of ivermectin with the combined treatment of darunavir/ritonavir and hydroxychloroquine among asymptomatic and adult COVID-19 patients (NCT04435587).

Atazanavir

Atazanavir is a viral protease inhibitor used for the treatment and prevention of HIV.³⁹ Previous studies have suggested its bioavailability within the upper respiratory tract, this has impelled it an interesting molecule for the treatment of SARS-CoV-2. A randomized phase III clinical trial has been initiated in Iran to compare the therapeutic potential of atazanavir/ritonavir with lopinavir/ritonavir (IRCT20200504047298N1) and lopinavir/hydroxychloroquine (IRCT20100228003449N30). Moreover, another clinical trial of atazanavir is also ongoing in combination with NA-831 and dexamethasone (NCT04452565).

Nelfinavir

Nelfinavir is an effective viral protease inhibitor of HIV.⁴⁰ It has been reported previously that nelfinavir impedes the replication of SARS-associated coronavirus.⁴¹ Therefore, the anti-SARS potential of the Nelfinavir makes it a good lead compound for designing the therapeutic regimen of COVID-19 patients. A clinical trial in Japan has been initiated to evaluate the efficacy of nelfinavir for asymptomatic or mild COVID-19 (jRCT2071200023).

Viral Nucleoprotein (N protein) Inhibitors

Nitazoxanide

Nitazoxanide is an antiparasitic and antiviral drug. It

shows *in vitro* inhibitory activity against coronaviruses including the Middle East respiratory syndrome (MERS) coronavirus by halting the viral nucleoprotein (N protein) expression. It also reduces the release of pro-inflammatory cytokines.⁴² Due to its profound antiviral activity against other coronaviruses, nitazoxanide is a prospective drug candidate for the treatment of coronavirus patients. A randomized phase II clinical trial was initiated in July 2020 to investigate the efficacy of nitazoxanide as a medication for SARS-CoV-2 patients (NCT04423861). Another phase III clinical trial was launched to investigate the effectiveness of nitazoxanide (NCT044441398). Several clinical trials are ongoing for the investigation of the antiviral potential of nitazoxanide against COVID-19 in India (CTR1/2020/06/025849), the United States (NCT04486313), Nigeria (NCT04459286), and Argentina (NCT04463264).

In addition to this, some other clinical trials have also been initiated to analyze the therapeutic potential of nitazoxanide as a prophylactic agent in COVID-19 in the US (NCT04343248, NCT04359680), Brazil (NCT04435314), and Mexico (NCT04406246).

Summary

Several FDA approved drugs that are originally indicated to treat infection of viruses other than SARS-CoV-2 have shown promise in the COVID-19 patients in multiple clinical trials in different counties, It is important that repurposing of the existing drugs should be emphasized because of the sense of urgency and their advantages related to cost, time, and safety.

REFERENCES

1. Fan HH, Wang LQ, Liu WL, An XP, Liu ZD, He XQ, et al. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Chinese medical journal. 2020; 133:1051-6.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020; 395:565-74.
3. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. 2020: 102433.
4. McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacological Research. 2020: 104859.
5. European Centre for Disease Prevention and Control.

- [Available from: <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>.
6. Organization WH. 2020 [Available from: <https://covid19.who.int/>].
 7. Government of Pakistan. [Available from: <http://covid.gov.pk/>].
 8. Villalain J. Membranotropic effects of arbidol, a broad antiviral molecule, on phospholipid model membranes. *The journal of physical chemistry B*. 2010; 114: 8544-54.
 9. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. *The Journal of infection*. 2020;81(1):e1-e5.
 10. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *MedRxiv*. 2020.
 11. Chen W, Yao M, Fang Z, Lv X, Deng M, Wu Z. A study on clinical effect of Arbidol combined with adjuvant therapy on COVID-19. *Journal of medical virology*. 2020.
 12. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). *MedRxiv*. 2020.
 13. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *Journal of Infection*. 2020; 81: e21-e3.
 14. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo [2, 1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. ACS Publications; 2017.
 15. Wu R, Wang L, Kuo HCD, Shannar A, Peter R, Chou PJ, et al. An update on current therapeutic drugs treating COVID-19. *Current Pharmacology Reports*. 2020: 1.
 16. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*. 2020.
 17. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020.
 18. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19—preliminary report. *New England Journal of Medicine*. 2020.
 19. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *New England Journal of Medicine*. 2020.
 20. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan Academy, Series B*. 2017; 93: 449-63.
 21. De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. *Chemistry—An Asian Journal*. 2019; 14: 3962-8.
 22. Lou Y, Liu L, Qiu Y. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial. *medRxiv*. 2020.
 23. Bhatia HK, Singh H, Grewal N, Natt NK. Sofosbuvir: A novel treatment option for chronic hepatitis C infection. *Journal of pharmacology & pharmacotherapeutics*. 2014; 5: 278.
 24. Parker WB. Metabolism and antiviral activity of ribavirin. *Virus research*. 2005; 107: 165-71.
 25. Hung IFN, Lung KC, Tso EYK, Liu R, Chung TWH, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *The Lancet*. 2020; 395: 1695-704.
 26. Chan KW, Wong VT, Tang SCW. COVID-19: An update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese–Western medicine for the management of 2019 novel coronavirus disease. *The American journal of Chinese medicine*. 2020; 48: 737-62.
 27. Korba BE, Furman PA, Otto MJ. Clevudine: a potent inhibitor of hepatitis B virus in vitro and in vivo. *Expert review of anti-infective therapy*. 2006; 4: 549-61.
 28. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs*. 2001; 61: 263-83.
 29. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*. 2020; 323: 1061-9.
 30. gov NUSNLoMC. 2020 [Available from: <https://clinicaltrials.gov/ct2/show/NCT04338698>].
 31. Wang RR, Yang QH, Luo RH, Peng YM, Dai SX, Zhang XJ, et al. Azvudine, a novel nucleoside reverse transcriptase inhibitor showed good drug combination features and better inhibition on drug-resistant strains than lamivudine in vitro. *PLoS One*. 2014; 9: e105617.
 32. Ren Z, Luo H, Yu Z, Song J, Liang L, Wang L, et al. A Randomized, Open-label, Controlled Clinical Trial of Azvudine Tablets in the Treatment of Mild and Common COVID-19, A Pilot Study. *Advanced Science*. 2020: 2001435.
 33. Frampton JE, Croom KF. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate. *Drugs*. 2006; 66: 1501-12.
 34. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. *International journal of antimicrobial agents*. 2009; 33: 307-20.
 35. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*. 2020.
 36. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR. *Journal of Korean medical science*. 2020; 35: e79.
 37. Busse KH, Penzak SR. Darunavir: a second-generation protease inhibitor. *American journal of health-system pharmacy*. 2007; 64: 1593-602.
 38. Chen J, Xia L, Liu L, Xu Q, Ling Y, Huang D, et al., editors. Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19. *Open forum infectious diseases*; 2020: Oxford University Press US.
 39. De Clercq E. Antiviral drugs in current clinical use. *Journal of clinical virology*. 2004; 30: 115-33.

40. Lewis II JS, Terriff CM, Coulston DR, Garrison MW. Protease inhibitors: a therapeutic breakthrough for the treatment of patients with human immunodeficiency virus. *Clinical therapeutics*. 1997; 19: 187-214.
 41. Yamamoto N, Yang R, Yoshinaka Y, Amari S, Nakano T, Cinatl J, et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. *Biochemical and biophysical research communications*. 2004; 318: 719-25.
 42. Rossignol J-F. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *Journal of infection and public health*. 2016; 9: 227-30.
-