



Pharmacodynamics of Remdesivir: How to Improve for COVID-19 Treatment

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ABSTRACT

Potential clinical benefit in SARS-CoV-2 infection upon remdesivir treatment has been established. Recently, FDA has granted full approval for the clinical use of remdesivir for COVID therapy. However, the efficacy of remdesivir alone or in combination with other antivirals is still open to research, especially in terms of benefits vs. risk ratio. We here review remdesivir therapy based on a search for relevant pharmacological evidences with regards to the Pharmacokinetics (PK) and Pharmacodynamics (PD) of appropriate antiviral compounds against COVID-19 alone or in combination with other potential therapies. Drug-Drug Interactions (DDIs), if any in case of combo treatments have also been taken into consideration. We found promising *in vitro* evidence for efficacy of remdesivir, in combination with (hydroxy) chloroquine and/or favipiravir against SARS-CoV-2 infection in cell culture studies. However, clinical trial results from these combinations were not in line with the promising *in vitro* data, and therefore limit the use of such combinations in practice. Remdesivir and antibody therapies have also been used clinically either in combination or in sequential application. However, there are no substantive evaluable clinical data on these uses as of now. Additionally, some other drug combinations with remdesivir have been proposed in this article for future improvement in therapies.

ABBREVIATIONS

ARDS: Acute Respiratory Distress Syndrome; AUC₂₄: Area Under the Plasma Concentration-Time Curve from Time Zero To Time 24 H; CSF: Cerebrospinal Fluid; DDI: Drug-Drug Interactions; EPASG: European PK/PD Anti-Infective Study Group; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; ECMO: Extracorporeal Membrane Oxygenation; FDA: Food and Drug Administration; FIP: Feline Infectious Peritonitis; Ifns: Interferons; Pegifn: Pegylated Interferon; LOQ: Limit of Quantification; LPV/R: Lopinavir/Ritonavir; MERS: Middle East Respiratory Syndrome; P-Gp: P-Glycoprotein; PK: Pharmacokinetics; PD: Pharmacodynamics; RCT: Randomized Control Trial; RDV: Remdesivir; Rdrp: RNA Polymerase; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TDM: Therapeutic Drug Monitoring; Vd: Volume of Distribution.

INTRODUCTION

Drugs active against SARS-CoV-2

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that causes COVID-19 was declared as a global pandemic on 11 March 2020, by the WHO, however, the evidence for therapies against this virus is as yet inadequate. Various medical teams are prescribing drugs for this collection of ailments based on some mechanistic data but with limited clinical findings in support of their activity. The

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DOI: 10.37871/jbres1175

Submitted: 17 December 2020

Accepted: 21 December 2020

Published: 22 December 2020

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OPEN ACCESS

Subject: Medicine Group

Topic & Subtopic(s): Therapeutics, Pharmacology

Keywords

- Remdesivir
- COVID-19
- Pharmacodynamics
- Pharmacokinetics
- Antivirals

clinical utility of preclinically validated dosing regimens relies heavily on the available Pharmacokinetic (PK) data used in the computer simulations performed to support such use for the particular drug [1].

Therapeutic agents available for COVID-19 can have other treatment challenges, particularly drug-drug interactions. Several compounds that have been proposed for the treatment of SARS-CoV-2 are affected by the Cytochrome P450 (CYP)-metabolizing system as an either substrate, enzyme inhibitor or enzyme inducer [2]. Therefore, the dosing requirements of concomitant SARS-CoV-2 or other supportive drug therapies should be evaluated properly based on the above-mentioned possible drug-drug interaction, at least for non-novel compounds. For example, Lopinavir/Ritonavir (LPV/r), a strong inhibitor of CYP3A4 and CYP2D6, can metabolize hydroxychloroquine (an antiviral against SARS-CoV-2) and therefore exhibited a potential toxicity in an animal model [2].

Remdesivir, formerly known as GS-5734, is a nucleotide analogue that is claimed to have been originally developed as a treatment against Ebola [3]. This drug can also inhibit corona virus replication by inhibiting RNA polymerases (RdRp4). This compound has shown broad antiviral activity *in vitro* against Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), and SARS-CoV-2 [4-6].

Animal studies

In animal studies, remdesivir has been found effective in protecting rhesus monkeys from MERS-CoV infection, when given prior to infection [7]. It also protected African green monkeys from Nipah virus, a cause of fatal encephalitis; and also rhesus monkeys from Ebola virus [8,9]. A randomized, well-marked, controlled animal study with 12 rhesus monkeys infected with SARS-CoV-2 reported that an attenuation of respiratory symptoms and reduction in lung damage with remdesivir administered 12 hours after virus infection [10].

SARS-CoV-2 virus enters host cells by binding to and fusing with cell membrane receptor, ACE-2, followed by membrane fusion. Once inside, the virus uses the host cell's machinery to replicate, using the virus's RNA Dependent RNA Polymerase (RdRp) for making genome and transcript copies. Among the different strains of the corona virus, this non-structural protein is unique in structure, and thus making it a potentially useful drug target. Sofosbuvir, a synthetic analogue of nucleosides and nucleotides which inhibits RdRp has led to a successful treatment for hepatitis C infection [11]. Based on these facts, remdesivir was approved by FDA in various clinical trials for the treatment of COVID-19 infected people [12].

However, efficacy of remdesivir *in vitro* or in animals does not match with the clinical outcomes in humans. Further, remdesivir has some side effects. In the Ebola trial, the side effects of Remdesivir (RDV) were possible liver damage

demonstrated in increased liver enzyme levels in plasma. Similar increases in liver enzymes in three U.S. COVID-19 patients were also documented after remdesivir treatment. Other typical antiviral drug side effects include Nausea and Vomiting [13]; and also affects kidney and mitochondria [14,15].

We searched for other compounds or drugs that could be used in conjunction with remdesivir to potentiate its effect against SARS-CoV-2 and that could minimize the side effects of remdesivir.

Search methodology

Drugs of interest were identified from literature search as listed in the (Table 1), and their PK/PD characteristics were reviewed (Table 2). Searches of the PubMed and Embase databases (no date limits) were performed to identify the clinical trials with those drugs of interest. Retrospective clinical studies, and animal and/or *in vitro* studies on the drug therapies are summarized in table 3. In addition, information on Drug-Drug Interactions (DDIs) were also noted [16]. The influence of extracorporeal support treatments on antiviral PK might also be necessary for critically ill patients with COVID-19, and is depicted in table 3.

List of potential antiviral agents for the treatment of COVID-19

The general information for some key drugs against COVID-19 are summarized in table 1. Most agents were originally approved for the treatment of other viral infections, except hydroxy-chloroquine that has been used for over 60 years primarily for malaria treatment, and is also approved for systemic lupus erythematosus [17].

RESULTS

Pharmacokinetics/Pharmacodynamics (PK/PD) of combo antiviral agents for the treatment of COVID-19

For a drug to be clinical effective, it's *in vivo* concentrations in tissues of interest and potentially in the blood stream as well, should exceed its antiviral effectiveness or inhibitory concentration values. Table 2 summarizes the viral inhibition data of some of the agents recommended for SARS-CoV-2. The available data are based on *in vitro* studies in various cell lines. The EC50 values for other viruses are compared against SARS-CoV-2, while EC90 is usually preferred only when the EC90 is nine-fold higher than EC50 [18].

The combo drug effect of remdesivir and ribavirin were tested on MERS-CoV and SARS-CoV. The EC50 values were higher in SARS compared to MERS, indicating that a higher dose of the drug would be needed to treat COVID-19 than for MERS. However, the EC50 value of chloroquine was within the same range for SARS-CoV-2 and MERS. Since EC50 is not a time-dependent parameter, this data

Table 1: Some prospective Antivirals against COVID-19.

Generic name	Mode of action	Study phase	Approved doses (mg)	Route of Administration
Remdesivir	Viral RNA Polymerase Inhibitor	Phase III/IV	200 mg on day 1, followed by 100mg/Day on days 2-10	IV
Chloroquine	Inhibits endosome-mediated viral entry; and pH-dependent steps in viral replication [36]	Phase III/IV	600 mg/12 hr on day 1, followed by 300mg bid on days 2-5. OR: 500 mg/12 hr over 5 days [37]	PO or IV
Hydroxychloro- quine	Same as Chloroquine	Phase III/IV	400 mg/day for 5 days, OR 400 mg/ 12 hr on day 1 followed by 200 mg/12 hr on days 2-5 [37]	PO
Lopinavir (LPV) / Ritonavir	HIV: Protease inhibitor	Phase IV	LPV: 400 mg/12 hr Rito: 100 mg/12 hr [38]	PO
Favipiravir	Viral RNA Polymerase Inhibitor	Phase III	Under study	PO, IV [39]
Ribavirin	Multiple possible mechanisms	Phase II	500 mg/12 h or 500 mg/8h IV [40]	Aerosol, PO or IV
IFN- α 1 β	Adjuvant treatment: Enhancement of phagocytic/ cytotoxic mechanisms	Early Phase I	10 μ g/12 hr	Nebulized
IFN- α	Same as IFN- α 1 β	Not applicable	5 million IU/12 h [41]	Nebulized
IFN- β 1 β	Same as IFN- α 1 β	Phase II	25 μ g SC inj. alternate day for 3 days	SC
Camostat	Blocks interaction between the S1 protein and SARS-CoV-2 target cell	Phase I/II/III	200 mg/12 or 8 hr	PO
Nafamostat	Same as Camostat	Phase II	20-50 mg IV [42]	IV

PO: Oral; IV: Intravenous; SC: Subcutaneous

Table 2: PK/PD of Some Antivirals against COVID-19.

Drug/ Generic name	IC50	Type of study	EC50/EC90 (μ M) For COVID-19	Blood Concentrations	Remarks
Remdesivir	EC50 EC90	<i>In vitro</i> (vero E6 cells)	0.77 [6] 23.15 [43] 1.76 [6]	10 μ M in non-human primates was reached after a dose of 10 mg/kg IV.	Treatment outcome is similar to CoVID-19 patients [40]
Chloroquine	EC50 EC90	<i>In vitro</i> (vero E6 cells)	1.13 -7.36 [6] 6.9 [6]	A concentration of 6.9 μ M is achievable in patients after a 500 mg dose [6,45]	Adverse effects were found with 600 mg/12 h for 10 days compared to 450 mg/12h on day 1 and once daily between days 2 and 5 [46]
Hydroxychloro quine	EC50	<i>In vitro</i> (vero E6 cells)	0.72 [37] 4.51 - 12.96 [20]	Conc. >1.49 μ M (>500 ng/mL) achievable following a 6 mg/kg/day dose [51]	Treatment outcomes were no different from standard care of hospitalized COVID patients [52]
Lopinavir/ Ritonavir	EC50	<i>In vitro</i> (vero E6 cells)	LPV: 26.63 [43]	LPV Cmax average 12.72 μ M and Ritonavir Cmax average 0.7 μ M [49]	Treatment outcomes were no different from standard care of hospitalized patients with COVID-19 [50]
Favipiravir	EC50	<i>In vitro</i> (vero E6 cells)	61.88 [6] >100 [43]	Conc. of 1190 \pm 478 μ M were achieved after 1 h of 400 mg dose in non-human primates [51]	Faster viral clearance and radiological improvement was reported in patients received Favipiravir compared to Lopinavir/ Ritonavir [52]
Ribavarin	EC50	<i>In vitro</i> (vero E6 cells)	109.50 [6] >100 [43]	Conc. range between 25 and 10.65 μ M achieved with a ribavirin dose of 400-600 mg/12 h [53]	
IFN- β 1 β	EC50 EC90	Not available	Not available	Conc. 240 UI/mL following 8 million IU SC [54]	
Camostat	EC50 EC90	<i>In vitro</i> (Calu-3 cells)	0.087 - 1 [55,56] 5 [55]	Conc. 589 μ M was achieved 12 h after Camostat 40 mg IV administration in humans [57]	
Nafamostat	EC50	<i>In vitro</i> (Calu-3 cells)	0.005 [56]	Conc. 41, 116, and 174 μ M were achieved 12 h after Nafamostat 10, 20 and 40 μ M, IV, administration in humans, respectively [58]	

may not be reliable in an *in vitro* target (i.e. as a clinical parameter) [19]. Furthermore, other studies have found that while chloroquine was though more potent than hydroxychloroquine, both result in an increased mortality when used in COVID-19 [20]. These drugs have cardiac side effects which are likely to be responsible for the increased mortality.

Several Interferons (IFNs), including IFN- α , PegIFN- α 2 β , IFN- α 1 β and IFN- β 1 β , have been examined for the treatment of COVID-19 as an adjuvant therapy with other anti-COVID-19 drugs. However, the drug efficacy and PK/PD targets for COVID-19 are not available, only some data on plasma concentrations are available in the literature (Table 2).

Table 3: Drug-Drug Interactions of some prospective antivirals against COVID-19.

Combination of Drugs	Pharmacodynamic Rationality	Effects of drug-drug Interactions	Types of Evidences	Therapeutic Comments
Ribavirin + Lopinavir [59]	Inhibition of Viral RNA synthesis and their replication	Increased risk of liver toxicity	Retrospective clinical data [21,60] <i>In vivo</i> animal data [61]	Monitoring for Liver toxicity
Chloroquine + Lopinavir	Inhibition of Viral entry and their replication	Increased risk QTc prolongation. Inhibition of CYP3A-mediated metabolism of chloroquine by <i>ritonavir</i>	Retrospective clinical data: No data yet <i>In vivo</i> animal data, or any <i>in vitro</i> data: Not yet	Monitoring for ECG, and for increased toxicity. Dose reduction of chloroquine might be necessary in such a case.
Favipiravir + Interferon	Inhibition of viral RNA synthesis and immune modulation	No data	Clinical trials: No data <i>In vivo</i> animal data, or any <i>in vitro</i> data: Not yet	None
Interferon + Ribavirin	Immune modulation and Inhibition of viral RNA synthesis	No data	Clinical trials: Ongoing [62] <i>In vivo</i> and <i>in vitro</i> data: Synergistic antiviral effect were described elsewhere [61-64].	
LPV/r +Interferon +Ribavirin	Immune modulation, Inhibition of viral RNA synthesis, plus inhibition of replication	Level of severity: Major	Clinical trials: The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab, and shorter duration of hospitalization than the control group [65] <i>In vivo</i> and <i>in vitro</i> data: Not yet	Monitoring for Liver toxicity

Search for any Drug-Drug Interaction (DDI) during combination of SARS-CoV-2 antiviral agents

LPV/r plus ribavirin therapy resulted in a reduction in mortality, Acute Respiratory Distress Syndrome (ARDS), and viral shedding in the treatment of SARS (Table 3). Another HIV protease inhibitor, nelfinavir, exhibited good activity against SARS [21,22], but are less effective against MERS [23]. Combination of LPV/r, ribavirin and IFN resulted in a shorter duration of viral shedding and hospital stay when compared with LPV/r alone. Randomized trials involving these drugs are yet, to be known.

The newer investigational antiviral agents, remdesivir and favipiravir, appear to have a lower potential for DDIs; however, the main concern with their use is the decrease in the drug concentrations if co-administered with CYP-enzyme inducers. A comprehensive and evolving DDI database has been created by the University of Liverpool and this should be consulted for potential DDIs, if needed [2].

Improvement of Antiviral activity of Remdesivir against SAR-CoV-2

FDA authorizes second COVID-19 treatment drug to be used in combination with remdesivir [24]. Baricitinib is a Janus Kinase Inhibitor (JAK), which blocks the activity of one or more of a specific family of enzymes, interfering with the pathway that leads to inflammation. Baricitinib is FDA-approved oral medication for severely active rheumatoid arthritis. In a clinical trial of hospitalized patients with COVID-19, baricitinib, in combination with remdesivir, was shown to reduce recovery time from 8 to 7 days compared to placebo and remdesivir (18 days of recovery) [25]. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated.

Concerns exists that Angiotensin-Converting Enzyme Inhibitors (ACE-Is) and Angiotensin Receptor Blockers

(ARBs) may increase susceptibility to coronavirus SARS CoV [26]. There is also widespread speculation about the potential benefits of ACE-Is and ARBs, based on biological plausibility arguments and animal data and small clinical studies on patients with other viral respiratory infections [27].

A new study by researchers at Germany’s Jülich Research Centre reports that a hexapeptide can inhibit the aggregation and activation of the Spike (S) protein of SARS-CoV-2. *In vitro* experiments have shown that this peptide prevented the infection of cells in culture by SARS-CoV-2. Additionally, it has been found that this peptide also prevents another coronavirus, h-CoV-NL63, from replicating inside the cells. Further, the hexapeptide is also highly specific for the S protein, and therefore can be considered for development as a potential drug either alone or in combination with remdesivir [28].

DISCUSSION

Remdesivir is a RNA polymerase inhibitor and it inhibits infection of SARS-CoV-2 virus in a human cell line, *in vitro* [6]. In an animal model of SARS-CoV and MERS-CoV infections, Remdesivir also showed decreased viral load and improved pulmonary function [5]. These data, together with the human safety profile data from intravenous remdesivir therapy of Ebola virus disease are the basis for the use of remdesivir intravenously for COVID-19 therapy in humans [3,29]. After intravenous administration, in two critically ill Chinese patients with severe adult respiratory distress syndrome, remdesivir showed a peak at the end of infusion and a half-life of 1 h, while GS-441524 (a plasma metabolite of remdesivir, that also has antiviral activity though very limited, compared to remdesivir) reached a peak 1 h after infusion and then remained detectable until the next remdesivir administration [30]. Similar data have been shown in rhesus monkeys infected with SARS-CoV-2, where

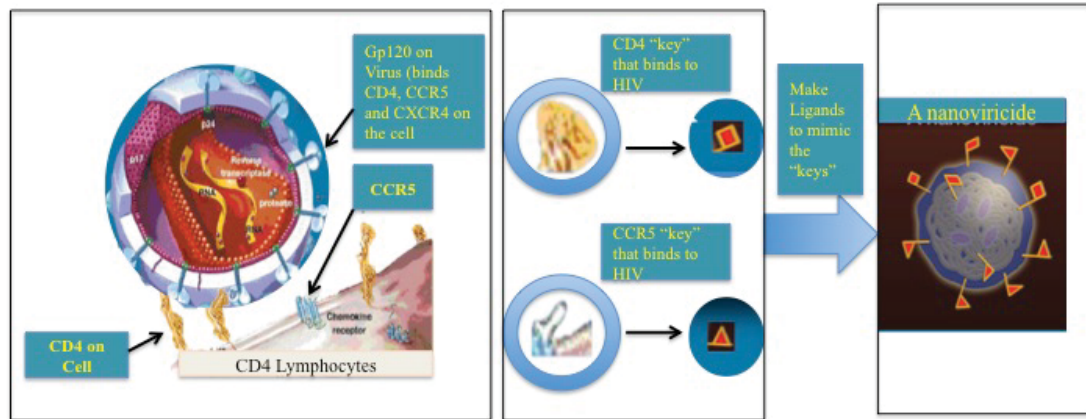


Figure 1 Novel Platform Technology: Nanoviricide is a Cell Mimic.

HIV Particle Binding to a Cell via CD4 and Co-receptor.

A *nanoviricide* "looks like" a human cell to the virus. *Nanoviricide* is large enough for a virus particle to latch onto it. Yet small enough to circulate readily in the body. Rather than the virus particle entering into a *nanoviricide*, a *nanoviricide* wraps around the virus particle and encapsulates it, by using the virus particle's very same ability to enter a cell.

Viral Resistance to the *Nanoviricide* drug is unlikely because even as the virus mutates, it still binds to the same cell surface receptor(s), in the same fashion.

the intravenous administration of remdesivir which was converted into the nucleoside analogue GS-441524, reached and sustained to its EC90 values [6,9,29,31].

Remdesivir is metabolized by non-specific esterases in the blood stream as well as inside cells to GS-441524. While remdesivir contains a 5'-phosphate, and thus would become rapidly converted to the active triphosphate nucleotide analog inside cells via non-specific pyrophosphorylases and kinases, the metabolite GS-441524 must go through the rate-limiting slow step of first phosphorylation with a nucleoside kinase. GS-441524 therefore exhibits substantially weaker activity compared to remdesivir *in vitro*. Thus conversion to weakly active form *in vitro* potentially limits the clinical activity of remdesivir and accounts for its poor clinical response compared to its significantly strong *in vitro* efficacy. Thus, improvement in PK/PD of remdesivir in terms of protection from esterase metabolism may significantly improve its clinical efficacy.

These preliminary observations improve knowledge about the PK and use of remdesivir for treatment of COVID-19 patients. However, further studies, with greater numbers of patients, and clinical trials, are needed to confirm these preliminary results, along with other strategies to strengthen the combo effects of remdesivir and other novel candidates. In particular, WHO recently suggested that retrospective analysis of remdesivir treatment did not show significant benefits, in contrast to what was observed in controlled clinical trials [32]. Remdesivir (Veklury, Gilead) is supplied as a lyophilized solid containing 100 mg remdesivir and 600 mg SBECD (sulfobutylether- β -cyclodextrin) which requires to be redissolved in WFI water by the Pharmacist, and injected into infusion fluid (saline) preferably through a sterile filter [https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=98b7e6bf-2668-4a61-a874-194eb674b15c&version=7#!]. It is likely that the

redissolution may not be complete, and filtration may be removing undissolved remdesivir, thus reducing the dose applied, especially in the hands of inexperienced personnel during this pandemic. This could explain the discrepancy between the remdesivir controlled clinical trials and the WHO datasets. Cyclodextrins form colloids at high concentrations and allow insoluble drugs to be held in the colloid. However, the colloid dilutes out into the bloodstream quickly and would lead to falling out of the API if it is not held by a true cage-binding mechanism. Thus, in addition to protecting remdesivir from metabolism, keeping it in an encapsulated form physiologically is essential if its full potential (as observed in cell culture studies) is to be realized clinically.

NanoViricides, Inc. at Shelton, CT, are working to protect the remdesivir by encapsulation in a polymer to guard from degradation in the blood stream and also for slow release to minimize the side effects [33]. Besides, NanoViricides, Inc. has also developed a platform technology such that a when a virus encounters our nanoviricide® bio-mimetic polymer, the virus particle would bind to and would get engulfed into the polymeric nanoviricide, acting like a "Venus-fly-trap", and the virus particle would get destroyed in the process (Figure 1). Using a plug-and-play approach, we can change the virus binding ligand portion of this nanomedicine to attack a different virus. We have already tested several drug candidates for broad-spectrum anti-coronavirus effectiveness in cell culture studies. One of the coronavirus strains (h-CoV-NL63) that we studied, uses the same cell surface receptor ACE2 (angiotensin converting enzyme-2) that is shared by SARS-CoV-2 and SARS-CoV-1. Out of our several test drug candidates, one drug showed as much as 15-times more effectiveness than favipiravir against two different coronaviruses (h-CoV-NL63 and HCoV-229E) in this study. Safety and Tolerability of that anti-coronavirus drug candidate was studied in an animal model, and found to be safe and well tolerated. There were no clinical

signs of immune or allergic reactions such as itching, biting, twitching, rough coat, etc. Further, there were no observable changes in any organs including large intestine or colon on post mortem in gross histology. This non-GLP safety/tolerability study was conducted under GLP-like conditions by AR BioSystems, Inc., Odessa, Tampa, FL. Further microscopic histology and blood work analyses are in progress [34].

SUMMARY

In summary, promising therapeutic options for COVID-19 are now emerging, while vaccines are being approved at a rapid rate. Continued evolution and emergence of distinctly different lineages and variants of the SARS-CoV-2 virus such as the lineage B.1.1.7, also called Variant of Concern VOC-202012/01 in the UK, and of 501.V2, among others, raises severe concerns regarding the ability of vaccines based on the original SARS-CoV-2 to remain effective. Same concern exists for the efficacy of antibody based drugs. The need for an effective treatment for infected patients thus looms large. The results from Randomized Controlled Trial (RCT) for remdesivir are encouraging and provide some direction for the treatment of COVID-19 patients [18]. Further to this, it is highly likely that one or more other agents mentioned in this review, in combination may emerge as a prophylactic or as an early treatment option to decrease the viral shedding, transmission, and/ or to reduce disease progression.

From a PK/PD perspective, drug development should not focus on the discovery of new treatment options alone, but should also help to investigate common key aspects, particularly the following.

- The optimal time point to start antiviral therapy, and required duration of therapy.
- The role of the individualization of therapy based on dose adaptation and Therapeutic Drug Monitoring (TDM) in the treatment of COVID-19.

In brief, this comparative analysis found that remdesivir treatment is associated with significantly lower mortality and higher recovery than any other standard treatment without remdesivir in patients with severe COVID-19 [35]. Improvement in its clinical effectiveness may be possible if its PK/PD characteristics can be improved, for example, if it can be protected from initial metabolism in the blood stream. Further ongoing research will reveal more information in the near future. Meanwhile, public health measures continue to be the best tools for containment of the COVID-19 epidemic worldwide. Given the rate of variant emergence, it would not be advisable to rely on vaccination to replace these measures, at least until highly effective broad-spectrum therapeutics become available. It is advisable to avoid infection by appropriate social distancing, use of face masks, and cleanliness protocols including hand washing. Furthermore, the use of PCR-based diagnostic tests and contact tracing continue to be important for limiting the spread of infection.

COMPETING INTERESTS

Both the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The study received funding from Nanoviricides, Inc.

AUTHORS' CONTRIBUTION

Both the authors contributed equally to prepare this article, read and approved the final manuscript.

ACKNOWLEDGEMENT

We would like to thank our colleagues for their help during writing this article.

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How to cite this article: Chakraborty A, Diwan A. Pharmacodynamics of Remdesivir: How to Improve for COVID-19 Treatment. *J Biomed Res Environ Sci.* 2020 Dec 22; 1(8): 431-438. doi: 10.37871/jbres1175, Article ID: JBRES1175