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REVIEW ARTICLE

Scoping insight on antiviral drugs against COVID-19

Ahmed S. Ali [a,b,*], Ibrahim M. Ibrahim [a], Abdulhadi S. Burzangi [a], Ragia H. Ghoneim [d], Hanin S. Aljohani [a], Hamoud A. Alsamhan [a,c], Jehan Barakat [a]

[a] *Department of Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*
[b] *Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Egypt*
[c] *Department of Pharmacology, Faculty of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia*
[d] *Pharmacy Practice Department, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia*

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KEYWORDS

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Abstract *Background:* COVID-19 is an ongoing viral pandemic produced by SARS-CoV-2. In light of *in vitro* efficacy, several medications were repurposed for its management. During clinical use, many of these medications produced inconsistent results or had varying limitations.

Objective: The purpose of this literature review is to explain the variable efficacy or limitations of Lopinavir/Ritonavir, Remdesivir, Hydroxychloroquine, and Favipiravir in clinical settings.

Method: A study of the literature on the pharmacodynamics (PD), pharmacokinetics (PK), safety profile, and clinical trials through academic databases using relevant search terms.

Results & discussion: The efficacy of an antiviral drug against COVID-19 is associated with its ability to achieve therapeutic concentration in the lung and intestinal tissues. This efficacy depends on the PK properties, particularly protein binding, volume of distribution, and half-life. The PK and PD of the model drugs need to be integrated to predict their limitations.

Conclusion: Current antiviral drugs have varying pharmacological constraints that may associate with limited efficacy, especially in severe COVID-19 patients, or safety concerns.

* Corresponding author at: Dept of Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
E-mail addresses: Profahmedali@Gmail.com, asali@kau.edu.sa (A.S. Ali).

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Contents

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by a highly infectious respiratory virus, SARS-CoV-2. It resulted in significant human and economic losses. About 181 million cases had been confirmed as of June 29, 2021, and 3.92 million verified deaths (Roser, et al., 2021; Ciotti, 2019; Chakraborty and Maity, 2020; Yang et al., 2020). Drug repurposing is the process of providing new uses for currently approved drugs. Some repurposed FDA-approved drugs were subjected to *in vitro* testing and showed promising results against SARS-CoV-2 (Touret et al., 2020; Saul and Einav, 2020). However, clinical trials of most antiviral drugs demonstrated inconsistent results or limitations (Siordia et al., 2020; Jomah et al., 2020). Limited publications were concerned with integrating pharmacokinetics/pharmacodynamics (PK/PD) parameters to predict their efficacy in clinical settings (Zeitlinger, 2020; Arshad et al., 2020). For an antiviral drug to be effective in treating COVID-19, it must achieve sufficient concentrations that suppress viral replication in multiple sites, primarily the cells of the upper and lower respiratory tract (Zhang et al., 2020). Wang; *et al.* suggested antiviral drugs, which showed activity against the virus *in vitro* and have high lung distributions, might benefit COVID-19 patients by reducing viral load (Table 1). The low concentration of unbound lopinavir (LPV) in the lung tissues limits its efficacy in COVID-19 patients (Wang and Chen, 2020).

The present review aims to provide a deeper understanding of the reasons behind variable efficacy or limitations of some antiviral drugs through the integration of their PK/PD and safety profiles. Four drugs were selected: Remdesivir (RDV), Lopinavir/ritonavir (LPV/r), Hydroxychloroquine (HCQ), and Favipiravir (FPV).

2. Remdesivir

2.1. Overview

RDV (Veklury) is a broad-spectrum antiviral drug RNA polymerase inhibitor (Fig. 1). It was initially developed in the United States to treat hepatitis C, but it was directed toward Ebola viral infection treatment. It is currently the first FDA approved antiviral drug against COVID-19. Only intravenous injection formulation is available, which needs patients to be

Table 1 Summary of some PD and PK variables of antiviral drugs (Wang and Chen, 2020).

Antiviral Drugs	EC_{50} [μM][a]	Distribution to lung & other tissues.	Lung/plasma drug concentration	Ability to reduce viral load in COVID-19[b]
Hydroxychloroquine	4.51	Lung & adrenal gland	51	Yes
Favipiravir	61.88–100	Lung & intestine	0.2	Yes
Lopinavir	26.1	Lung, stomach & intestine	0.5[c]	No
Remdesivir	0.11–0.77	Unknown	?	No

[a] Other values were reported.
[b] In nasopharyngeal swabs and/or oropharyngeal swab.
[c] The drug is 98% bound to plasma protein.

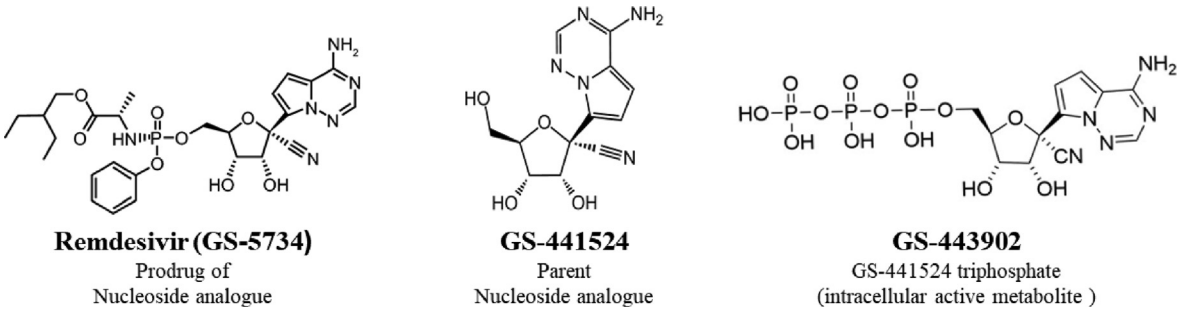

Fig. 1 Structure of RDV; the parent nucleoside analogue and final active intracellular metabolite.

hospitalized for administration. It is a prodrug that is expected to enable better intracellular delivery of an adenosine analog (GS-441524) monophosphate, which is then biotransformed into the active triphosphate intracellular metabolite (GS-443902) (Fig. 2) (Eastman et al., 2020; Amirian and Levy, 2020; Jorgensen et al., 2020).

2.2. Pharmacodynamics

RDV is an adenosine analog prodrug; within the cells, it is transformed into its active triphosphate metabolite that competes endogenous adenosine triphosphate to inhibit SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) ultimately inhibiting viral replication (Remdesivir, 2021).

Studies in VeroE6 cells demonstrated selectivity and high potency against SARS-CoV-2 demonstrated by its IC_{50} of 0.77 μM and an IC_{90} of 1.760 μM (Yang et al., 2020). However, a higher IC_{50} value of 23.15 μM was reported (Choy, 2020).

2.3. Pharmacokinetics

In monkeys, RDV demonstrated widespread tissue distribution and transformation into the final active metabolite (GS-443902) in both peripheral blood mononuclear cells and respiratory tissues (Deb, 2021). Animal PK studies revealed that renal and biliary excretion were the primary routes of elimination (Pardo, 2020). PK parameters of RDV and its major metabolite in humans are summarized in Table 2 (Remdesivir, 2021; Gordon et al., 2020; Singh et al., 2020; Ko, 2020).

RDV should be given by slow IV infusion, over 60 min. At the end of the infusion, peak concentration of RDV in the blood was reached; however, disappeared after 1 h. due to its rapid metabolism and distribution (Humeniuk, 2021). RDV has a high ability to bind to plasma proteins (88–93.6% bound). In contrast, the plasm protein binding of GS-441524 is as low as 2%. RDV is extensively metabolized in the liver and blood. The nucleoside metabolite GS-441524 is mainly excreted in the urine and most of the dose recovered in urine was as GS-441524 (48.6%) and about 10% of the RDV dose was recovered in the urine unchanged.

The intracellular activation of RDV was suggested or demeonstrated to involve several steps that end up by forming the final active nucleoside triphosphate (GS-443902) (Fig. 2).

The following data (Fig. 3) were based on RDV PK study in two severe COVID-19 patients, one of them has moderate renal dysfunction. On the first day, RDV was given as 200 mg loading dose then 100 mg daily. On days 3 through 9, blood samples were taken (after the end of IV infusion) immediately (C_0), 1 h. (C_1), and 24 h. (C_{24}). RDV serum concentration reached a peak (C_0), then began to decline to almost undetectable after 1 h. In contrast, the plasma concentrations of the metabolite GS-441524 peaked at C_1 and remained measurable until the next dose.

2.4. Clinical trials

Some early reports and meta-analyses suggested that RDV is not sufficient on its own for the management of COVID-19 in hospitalized patients (Alexander, 2020; Piscoya, 2020; Nasir, 2020). Later several meta-analyses suggested favorable benefit-risk profiles for RDV compared with placebo effects (Davies et al., 2020; Shrestha, 2021; Musa, 2020; Lai et al., 20212021; Frediansyah et al., 2021; Bansal, 2020). A recent meta-analysis concluded that RDV attenuates disease progression, leading to lower odds of mechanical ventilation/extracorporeal membrane oxygenation

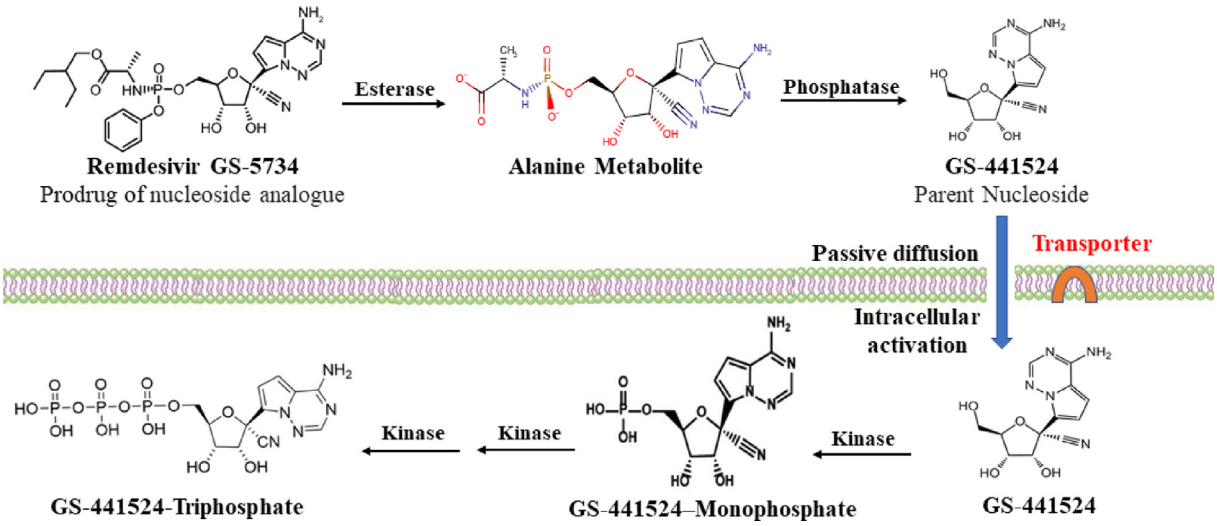

Fig. 2 *In vivo* bioactivation pathway of RDV (Yan and Muller, 2020), In the presence of serum enzymes, the phosphate prodrugs are hydrolyzed prematurely to the nucleoside. GS-441524, which after access to the cells activated to the triphosphate. Other pathway (not shown) involves, access of RDV into the cells, its metabolism to GS-441524 monophosphate, then to GS-441524 triphosphate.

Table 2 Pharmacokinetic Parameters of RDV and its major metabolite.

Parameter	RDV		GS-441524	
	1st day	5th day	1st day	5th day
C_{max} (μg/ml)	5.44	2.61	0.15	0.14
AUC (h* μg/ml)	2.92	1.56	2.24	2.23
$T_{1/2}$ h, mean (range)	0.98 (0.82–1.03)[a]	0.89	N/A	25.3 (24.1–30.3)[a]
Free fraction (%)	6–12		98	

On day 1, healthy volunteers received 200 mg RDV IV over 30 min, followed by 100 mg IV daily over 30 min on days 2 to 5. On the first day, AUC_{24} was presented, and on the fifth day, AUC tau was presented for GS-441524 and RDV, respectively. $T_{1/2}$ = half-life; AUC = area under the concentration–time curve.

[a] Adapted from (Grein et al., 2020).

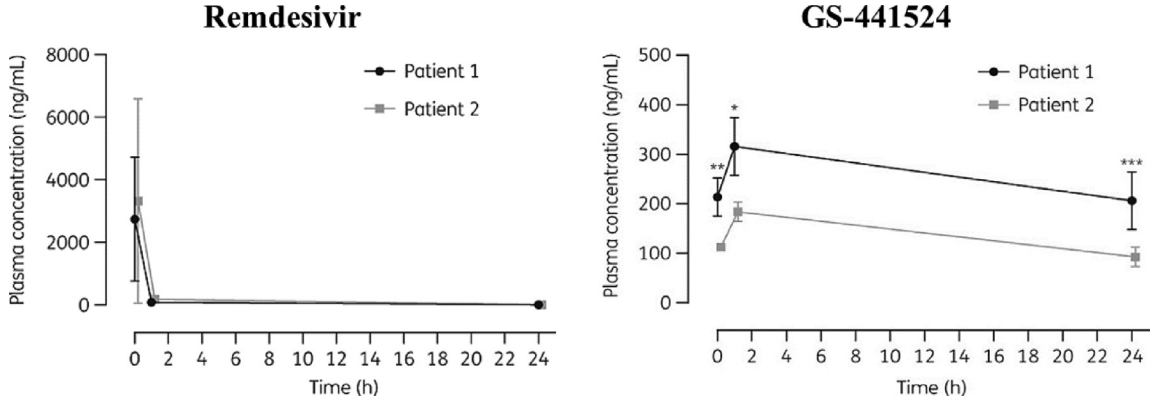

Fig. 3 RDV PK in critically ill patients after several doses of IV RDV. Left RDV, Right GS-441524 Patient 1 with renal impairment and Patient 2 without renal impairment; mean SD estimated 3–9 days after RDV initiation).

(MV/ECMO) and greater odds of hospital discharge for COVID-19 patients. However, RDV does not affect the odds of mortality (Reddy Vegivinti et al., 2021).

On the other hand, the WHO Solidarity Trial, which included 11,330 in-patients with COVID-19 who were randomized to receive HCQ (n = 954), LPV (n = 1411), RDV (n = 2750), interferon beta-1a regimens (n = 2063), or none of these drugs (n = 4088), found that all these investigated drugs had little to no effect on overall mortality (Consortium and W.S.T., 2021). However, RDV becomes the 1st FDA approved drug for the management of COVID-19 (Aleem and Kothadia, 2021).

2.5. Safety concern

Many adverse effects were reported for RDV during COVID-19 clinical trials, severe bradycardia being of particular concern, which is consistent with RDV's PD properties, (Touafchia, 2021), changes in ECG, anaphylaxis, infusion-related reactions, nephrotoxicity, and hepatic toxicity (Bistrovic and Lucijanic, 2021).

2.6. GS-441524 as an alternative to RDV

The oral bioavailability of GS-441524 in beagle dogs was investigated, and it was discovered that plasma concentrations up to 24-fold greater than the EC_{50} against SARS-CoV-2 could be maintained readily and safely. These findings support the development of GS-441524 as an oral COVID-19 treatment (Yan, 2021). Furthermore, GS-441524 effectively inhibited SARS-CoV-2 infection in mouse models (Li, 2021).

GS-441524 is a potent inhibitor of SARS-CoV-2 infected cells, with EC_{50} values on par with RDV (EC_{50} = 0.47–1.09 M), according to cell-based research (Pruijssers, 2020).

Moreover, there is evidence of fast metabolism of RDV in the blood into the parent molecule, nucleoside analog GS-441524. Moreover, the enzymes required for RDV metabolism and activation were more expressed in liver and kidney cells than in type ll pneumocytes in the lungs. Given these emerging data, it seemed logical to speculate that the anti-COVID-19 effect of RDV *in vivo* is mainly mediated through its parent compound GS-441524. Yan and Muller concluded that GS-441524 is thought to be superior to RDV in the management of COVID-19.

In addition, GS-441524 has a simplified synthesis method, easier to formulate as IV or inhalation (Yan and Muller, 2020). Moreover, RDV solution contains 6% sulfobutylated beta-cyclodextrin, which is likely to accumulate in patients with severe renal impairment (Remdesivir, 2021).

3. Lopinavir/ritonavir

3.1. Overview

LPV is an antiretroviral protease inhibitor (Fig. 4) indicated for the treatment of HIV-1 infection and has been repurposed to manage COVID-19. It is available as a fixed combination with ritonavir, a potent inhibitor of cytochrome P450-3A4, which allows LPV to be effective orally (Drożdżal, 2020; FURUTA et al., 2017).

3.2. Pharmacodynamics

LPV has been found to inhibits SARS-CoV-2 replication by binding to viral main protease 3C-like protease (3CLpro) with an EC_{50} of 16.7 μg/ml; however, other values have been reported (Vargas et al., 2020).

3.3. Pharmacokinetics

When administered alone, LPV has a low oral bioavailability of 25%; therefore, it is only given in combination with ritonavir, which increases its bioavailability by slowing its metabolism allowing therapeutic LPV concentrations to be obtained. After oral dosing, the maximal plasma concentrations of LPV/r are attained about 4.4 h; when taken with a meal, bioavailability increases (130% in the case of solution, 20% in case of tablets). The Vd after an oral dose is about 16.9 L (DRug-Bank(b). Lopinvair, 2021).

LPV is 98% bound to plasma proteins. Both alpha-1-acid glycoprotein and albumin are involved. LPV is mainly metabolized by hepatic CYP3A isozymes. Biotransformation is reduced and plasma levels of the active antiviral drug are enhanced when concomitantly taken with ritonavir, a potent inhibitor of CYP3A enzymes (DRug-Bank(b). Lopinvair, 2021).

3.4. Clinical trials

A meta-analysis concluded no significant advantage of LPV/r in alleviating symptoms of COVID-19 (Tobaiqy et al., 2020). Moreover, the WHO published results from the Solidarity Trial showed that LPV was not significantly different from control in reducing mortality or hospitalization. Similar results were confirmed by the Randomized Evaluation of COVID-19 Repurposed Antiviral Drugs for COVID-19 Therapy (RECOVERY) trial. Most protocols are now against its use in the management of COVID-19.

3.5. Limitations

At a dose of LPV/r 400 /100 mg twice orally, the steady-state peak (4 h. post-dose) and trough (before next dose) LPV concentration was about 18 μg/mL. Recall that its free level (unbound) was only about 1% (protein binding > 98%). Thus, the therapeutic free drug level (active form) is not achievable (Fig 5). Other limitations include its low Vd (about 17 L) and short half-life (about 7 h). As a result, only a tiny fraction

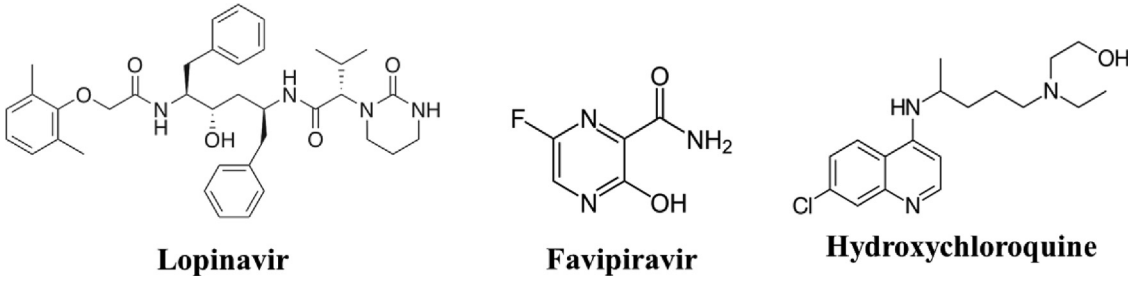

Fig. 4 Chemical structure of repurposed antiviral drugs.

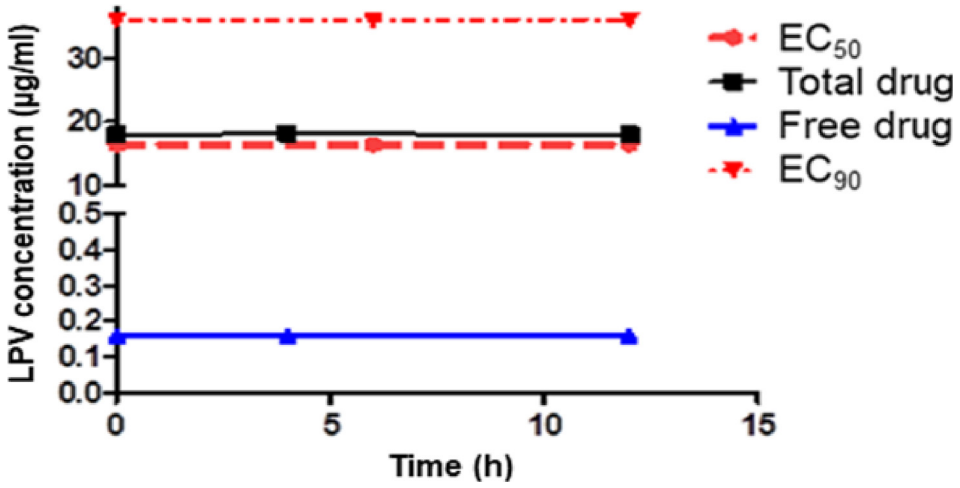

Fig. 5 Total and unbound LPV median peak and trough levels in COVID −19 patients. LPV/r 400/100 mg twice daily (Gregoire et al., 2020).

of the drug is available to enter the target lung cell. Indeed, a study by Cattaneo et al. suggested that the protein-adjusted IC_{90} values of LPV required to inhibit SARS-CoV-2 replication in plasma were 200-fold higher than the concentrations measured in blood samples obtained from COVID-19 patients (Cattaneo et al., 2021). This explanation for the ineffectiveness of the drug was the subject of several published studies.

Another critical limitation is that ritonavir, a potent inhibitor of cytochrome P450-3A4 is given in combination with LPV; therefore, a long list of interactions with other medications must be considered in COVID-19 patients (Sanders, 2020).

4. Favipiravir

4.1. Overview

FPV (T-705) is a modified pyrazine analogue (Fig. 4). It is a broad-spectrum antiviral RdRp inhibitor. It was developed in Japan and approved by the Pharmaceuticals and Medical Devices Agency (PMDA) to treat influenza. Also, it has been included in COVID-19 treatment guidelines in many countries (Chen et al., 2021; Cai et al., 2020).

4.2. Pharmacodynamics

FPV is a modified nucleoside analog that targets RdRp enzymes. It is a prodrug that undergoes intracellular activation to favipiravir-ribofuranosyl-5′-triphosphate (T-705-RTP) that binds to and inhibits RdRp, consequently inhibiting viral transcription and replication (Joshi et al., 2021). Wang, *et al.* reported low potency against SARS-CoV-2 (EC_{50} 61.88 µM) (Wang et al., 2020). However, other *in vitro* studies showed different EC_{50} values.

4.3. Pharmacokinetic

The drug is administered orally with a bioavailability of about 97%. FPV has non-linear PK demonstrated as a decrease in drug concentration after chronic administration. This may be explained by the auto-induction of certain CYP450 enzymes responsible for its metabolism (Madelain et al., 2016). Moreover, there is an ethnic variation in FPV's disposition (Hayden and Shindo, 2019; Nguyen, 2017).

4.4. Clinical ***trials***

FPV accelerates viral clearance by seven days and contributes to clinical improvement in about fourteen days. Particularly in patients with mild to moderate disease (Agrawal et al., 2020; Chen, 2020; Manabe et al., 2021). FVP treatment results in considerable clinical and radiological improvements compared to standard care, with no significant differences in viral clearance, need for oxygen, or side effect profiles. A study reported favorable outcomes when compared with umifenovir or LPV/r (Kaur, 2020). A randomized controlled trial in non-severe COVID-19 patients demonstrated that on day 7, FPV provided a better clinical recovery rate and was more effective than umifenovir in alleviating fever and cough.

4.5. Limitations

FPV is still under evaluation. Its PK/PD profile suggests potential effectiveness, at least, in mild and moderate cases of COVID-19. However, a PK study in critically ill COVID-19 patients who received the recommended dose of FPV demonstrated a low trough level (1 µg/mL) (Mohammad., 2020). Recall low potency against SARS-CoV-2 with EC_{50} 61.88 µM (Wang et al., 2020). The lung-to-tissue level of FPV was estimated to be about 50% of that in the blood. These PK data suggest moderate drug access to lung tissues (Irie, 2020). The drug did not show life-threatening adverse effects in clinical trials, but it has some adverse effects including a rise in serum uric acid, liver enzymes, diarrhea, nausea, vomiting, and tachycardia (Kaur, 2020). FPV may be teratogenic and has a long list of potential drug-drug interactions [Drug67].

5. Hydroxychloroquine

5.1. Overview

HCQ is a 4-aminoquinoline, similar to chloroquine (CQ) (Fig. 4) (Drug-Bank(c). Hyroxychloroquine, 2021). It is a low-cost drug that has been used to prevent and treat malaria and manage rheumatoid arthritis, lupus, and porphyria, among other conditions. (Johnson and Charnley, 1979; Browning, 2014; Filipova, 2021). It is usually taken orally as HCQ sulfate. The drug received extensive interest and debate due to its potential activity against COVID-19 (Saghir, 2021). Many African countries have already approved the use of HCQ or CQ to treat COVID-19 at the national level (Belayneh, 2020).

5.2. Pharmacodynamics

In vitro studies showed that HCQ is more potent than CQ against SARS-CoV-2 (EC_{50} of 0.72 μM for HCQ and 5.47 μM for CQ). As a result, HCQ was one of the earliest drugs to be tested against COVID-19. Regardless of the antiviral activity, HCQ has immunomodulatory effects (Hassan, 2019; Schrezenmeier and Dörner, 2020), which provided the basis of their utility to prevent cytokine release syndrome (CRS) (Hughes, 2018). Interestingly, HCQ has been suggested as a valuable drug for prophylaxis against lung thrombosis (Kravvariti, 2020).

5.3. Pharmacokinetics

Absorption of HCQ after oral administration is good but extensively variable (~70%; range: 25 to 100%). HCQ is considered a lysosomotropic drug that accumulates intracellularly at concentrations up to 1000-fold higher than the extracellular concentration. The rise in endosomal pH mediated by HCQ blocks virus/cell fusion. The elevated Golgi apparatus pH impairs the terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor and reduces its binding affinities to SARS-CoV-2 spike protein (Al-Bari, 2017; Shittu and Afolami, 2020). This accumulation in lysosomes is likely to explain the considerable very high volume of distribution of HCQ (Vd = 70 L/kg). The lung/plasma ratio of HCQ was suggested to be high, at least 50. HCQ has a long elimination half-life of about 40 to 50 days. These PK/PD characteristics explain the potential efficacy of HCQ against the novel virus (Derendorf, 2020; Zhou, 2020). HCQ is metabolized in the liver through CYP 2C3, 2D6, 2C8, 3A4, and 3A5 into active and inactive metabolites. Therefore, the genetic polymorphism of these enzymes would affect its blood level. About 20% of HCQ dose is excreted in urine as unchanged drugs; hence renal function is likely to affect its clearance (U.S. FDA, 2020). HCQ has a narrow therapeutic range and moderate protein binding (about 50%), primarily with albumin (Furst, 1996).

5.4. Clinical ***trials***

Million *et al*. reported the efficacy of HCQ/Azithromycin (AZ) in the early management of COVID-19. The study was conducted retrospectively and involved 1061 COVID-19 patients (Million, 2020). Yao *et al*. suggested optimized dosing regimens of HCQ for the treatment of SARS-CoV-2 based on the integration of its PD and physiologically based PK (PBPK) modeling and simulation. The authors simulated different dosing regimens and demonstrated that the ratios of HCQ lung concentration to the EC_{50} value would be approximately 20 to 170. These findings theoretically support the role of HCQ in the management of the COVID-19 (Yao et al., 20202020). Moreover, a cohort study in Saudi Arabia reported that HCQ had a modest effect on hospital length of stay in the ICU compared with standard treatment. Similar publications provided a similar impression of the potential benefit of HCQ in the management of COVID-19 (Gautret, 2020; Almazrou et al., 2020; Sahraei and Aminoquinolines against coronavirus disease, , 2019; Gao et al., 2020; Sarma et al., 2020).

According to a systemic review, HCQ was found beneficial in hospitalized COVID-19 patients when given early in the outpatient setting. HCQ is consistently effective against COVID-19, has not caused disease deterioration, and is well tolerated (Prodromos and Rumschlag, 2020)

In contrast, the WHO published the Solidarity Trial results showing that HCQ was not significantly different from control in reducing mortality or hospitalization (Pan, 2021). This was in line with RECOVERY trial that concluded: "there is no benefit of using HCQ in COVID-19 patients" (Horby et al., 2020).

5.5. Limitations

An *in vitro* study suggested that HCQ suppresses trained immunity, which is may be counterproductive to the antiviral innate immune response to SARS-CoV-2 (Rother, 2020). Lung acidosis that can be induced by severe COVID-19 is likely to reduce access of the weakly basic drug to lung tissues (Liu et al., 2016). Hence, HCQ has marked reduction in cellular uptake in severely ill patients (Geary et al., 1990). Consequently, Ali *et al*. suggested that HCQ is not likely to provide a potent antiviral effect in severe cases of COVID-19. If indicated, it should be given as early as possible to optimize its use (Ali et al., 2020). Another limitation of HCQ is potential QT prolongation and ventricular arrhythmia. Unfortunately, there has been no dose–response relationship study to accurately predict the association of HCQ drug level with cardiac toxicities (Horby et al., 2020; Javelot, 2020; Juurlink, 2020). Moreover, the drug showed extreme variability in drug levels in COVID-19 patients, as shown in Fig. 6.

6. Impact of pathophysiological changes, drug interactions and comorbidity

To ensure optimal use of medications in management of a disease; the integration of their PK/PD and side effects should be extended to include other variables such as genetic, chronic diseases, drug interactions, immunological status etc. A complex disease-drug-drug interaction is expected in severe COVID-19 (Kumar and Trivedi, 2021). Pathophysiological changes induced by severe COVID-19 include, hyperinflammation, severe hypoxia, acute respiratory distress syndrome

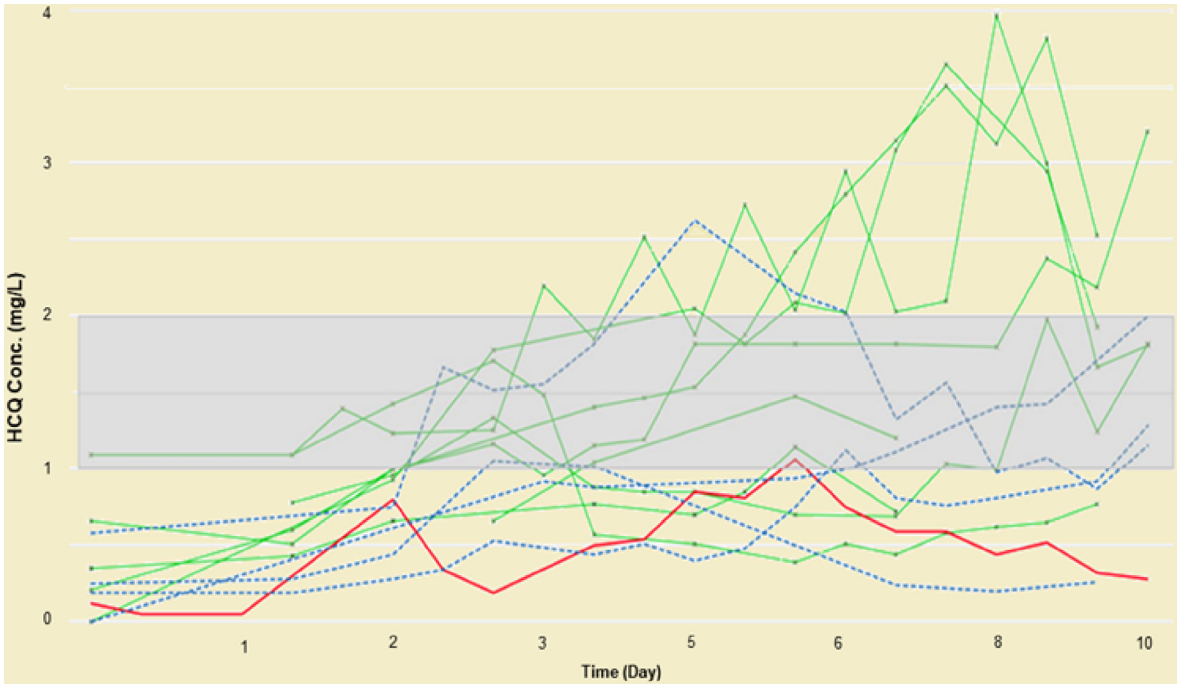

Fig. 6 PK of HCQ in COVID-19. Peak level after loading dose of 200 mg TID extremely variable [0.28–0.62], mean 0.5 ug/ml. Achievement of the assumed therapeutic level [1–2 ug/ ml] was delayed (Chakraborty and Maity, 2020; Yang et al., 2020; Touret et al., 2020; Saul and Einav, 2020; Siordia et al., 2020) mean 4 days. Potentially toxic level > 2 ug/ml was observed in some patients after 5 days (Painvin et al., 2020).

(ARDS), encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury (Polak et al., 2020) are likely to affect drug transporters, and its PK (Deb and Arrighi, 2021). For example, COVID-19 induced hypoxia and inflammation can reduce the intracellular transport of RDV main metabolite GS-441524 and its activation to GS-441524 monophosphate (Rasmussen, 2021).

COVID-19 associated complications also predispose the patients for drug induced toxicities (Nardo et al., 2021). For example, hypokalemia predisposes the patient to tachyarrhythmias, the cytokine storm is also known to prolong QT intervals (Kochav, 2020). This may explain the higher incidence of cardiac toxicity of antiviral drugs such as HCQ.

Pharmacotherapy of COVID-19 in patients with pre-existing comorbidities, especially elderly, is highly challenging due to the use of multiple medications with great potential for drug-drug interactions (Baburaj et al., 2021; Hodge et al., 20202020; Lemaitre et al., 2020; Rezaee, 2021). The PK properties (e.g., induction or inhibition of cytochrome P450 (CYP) isoenzymes, competition in renal elimination) as well as the PD properties (e.g., QT prolongation) are largely responsible for such drug–drug interactions. In addition to these interactions, COVID-19 patients have a significant pathophysiological changes, which can alter the PK of the medications (e.g., downregulation of CYP isoenzymes, organ failure, modification of plasma protein binding) (Morgan, 2009; Ofotokun et al., 2011).

Dosing of drugs used to treat COVID-19 in patients with renal or hepatic impairment requires great attention. Fortunately guidelines for dose adjustment and precautions are available in the drug monograph and some publications (Marra, 2020). For example, RDV should only be used in adults and children with an eGFR of less than 30 mL/min if the possible benefit justifies the potential danger (Adamsick et al., 2020).

Based on the genetics of COVID-19 patients, pharmacogenetics could explain the inter-individual variability in medication response. Variants in genes encoding drug-metabolizing enzymes, transporters, or receptors have been identified, and they may provide the information needed to develop a tailored therapy that optimize the use of pharmacotherapy for COVID-19 (Takahashi et al., 2020; Babayeva and Loewy, 2020; Zubiaur et al., 2020).

7. Inhaled formulations

Using a nebulizer with an inhaled nanoparticle formulation to deliver medications directly to the primary site of infection may allow for more targeted and accessible delivery in hospitalized and non-hospitalized patients, as well as potentially decrease systemic exposure to the drug. Inhaled nanoformulations of RDV is under development (Sahakijpijarn, 2021; Sun, 2020; CLINICAL-Trial.gov. Pharmacokinetics of Inhaled Nanoparticle Formulation of Remdesivir (GS-5734) and NA-831., 2021). Inhaled HCQ is also under investigation and showing promising results (Albariqi et al., 2021; Kavanagh, 2020; Klimke, 2020; Tai et al., 2021).

8. Summary and conclusion

Table 3 summarizes the PK/PD data of four repurposed antiviral medications. Even though all these medications displayed potency *in-vitro* against SARS-CoV-2, these

Table 3 Summary PK/PD of the specified antiviral drugs.

Repurposed drug	Antiviral mode of action	EC_{50}	EC_{90}	Lung/plasma ratio	Ion trapping	Impact of acidosis
Remdesivir (Wang et al., 2020)	Viral RNA polymerase inhibitor.	0.77 μM	1.76 μM	ND	Active metabolites	–
Lopinavir/Ritonavir (Cattaneo, 2020)	HIV protease inhibitor and a boost of other protease inhibitors.	16.7 μg/mL.	23.4 μM	0.5	No	–
Favipiravir (Driouich, 2021)	Viral RNA polymerase inhibitor	61.88 μM	52.5 μg/mL	0.2	No	–
Hydroxychloroquine (Gendrot, 2020)	Inhibition of pH-dependent steps in viral replication (Savarino et al., 2003)	E 1.5 μM.	3.0 μM	51	Yes	Reduced access to lung cells

preliminary findings do not always imply a consistent favorable clinical outcome in the treatment of COVID-19. A thorough assessment of the pharmacological profile from all angles, examining many factors impacting medication PK/PD and adverse effects such as drug interactions, genetics, chronic conditions, and so on, would allow a prior prediction of their usefulness or limitations in COVID-19 management. Developing an inhalable drug delivery system to optimize the use of these medications in management of respiratory viral infections is recommended.

9. Disclaimer

What was mentioned in this paper is a scientific view and information relating to general principles which should not be construed as specific instructions to change or criticize any protocols. But rather an academic discussion to push further research and development of these drugs for better achievements.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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