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REVIEW

Drug-drug interactions with candidate medications used for COVID-19 treatment: An overview

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Abstract

Drug-drug interaction (DDI) is a common clinical problem that has occurred as a result of the concomitant use of multiple drugs. DDI may occur in patients under treatment with medications used for coronavirus disease 2019 (COVID-19; i.e., chloroquine, lopinavir/ritonavir, ribavirin, tocilizumab, and remdesivir) and increase the risk of serious adverse reactions such as QT-prolongation, retinopathy, increased risk of infection, and hepatotoxicity. This review focuses on summarizing DDIs for candidate medications used for COVID-19 in order to minimize the adverse reactions.

KEYWORDS
adverse reactions, chloroquine, COVID-19, drug-drug interaction, Kaletra, remdesivir

1 | INTRODUCTION

Coronaviruses are responsible for major outbreaks of upper respiratory tract infections in both children and adults. On December 2019, novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, China.[1,2] COVID-19 can cause acute and highly virulence pneumonia. It has quickly spread from China to other countries.[2–5] COVID-19 infection is a major global problem that was documented more than 31 132 906 confirmed cases and approximately 962 008 deaths in the world.[6] On March 12, 2020, WHO declared COVID-19 outbreak a pandemic. Respiratory droplets and person-to-person contact are the most common transmission way. The incubation period of COVID-19 is about 2 weeks. The clinical diagnosis of COVID-19 is confirmed based on polymerase chain reaction technique.[7,8] The most common symptoms of COVID-19 are fever, dry cough, shortness of breath, and fatigue.[2,3] Gastrointestinal symptoms, such as diarrhea and nausea, have also been reported in several patients.[3,9,10] The overall fatality was reported <2% in patient without underlying disease but higher fatality observed in elderly patients

Abbreviations: AZA, azathioprine; COVID-19, coronavirus disease 2019; DDI, drug-drug interaction; IMPDH, inosine monophosphate dehydrogenase; RBV, ribavirin; RDV, remdesivir; TCZ, tocilizumab.

and patients with underlying disease (i.e., cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer).[11] The effective pharmacotherapy can reduce the mortality and morbidity of COVID-19.[12] Studies are recommended various combination therapy with chloroquine, lopinavir/ritonavir (Kaletra), ribavirin (RBV) and tocilizumab (TCZ) for the treatment of COVID-19.[13–16] On May 2, 2020, FDA approves emergency use of remdesivir (RDV) for COVID-19. One of the most important problems in pharmacotherapy is drug-drug interaction (DDI) which may significantly increase the adverse effects of drug. The present article focuses on reviewing DDIs of chloroquine, RBV, Kaletra, TCZ, and RDV to reduce side effects of COVID-19 treatment.

2 | RIBAVIRIN

Ribavirin (Virazole®), as a broad-spectrum antiviral drug, was approved by FDA in 1986 and administered as an aerosol for infants with respiratory syncytial virus infection.[17] RBV is a nucleos(t)ide analogue polymerase inhibitor which is used for the treatment of hepatitis C virus infection in combination with sofosbuvir and pegylated interferon alpha-2b.[18,19] The $t_{1/2}$, t_{max}, and bioavailability after a single oral dose of RBV (400 mg) is 1.5 h, 100 h, and 45%–65%, respectively.[20,21] Combination therapy with RBV and Xiyanping injection (the extraction of Andrographis paniculata) is widely used for inflammation and bronchitis in china.[22] Also, it used for viral hemorrhagic fever as off-label.[23,24] RBV is teratogenic and contraindicated in pregnancy (Category X). Also, it is necessary avoiding pregnancy during and 6 months after RBV therapy.[25] Dose adjustment is required in patients with renal and liver impairment. The absorption of RBV occurs in the proximal small intestine by Na^+-dependent nucleoside (N1) transporters.[26] It is not bound to plasma proteins. The commonly reported adverse effects of RBV were dyspnea (5%), headache (41%–69%), fatigue (25%–58%), anxiety (47%), apnea, hypotension, rash (15%–17%), and conjunctivitis (5%).

An interaction between RBV and warfarin was reported in a 61-year-old man under treatment with interferon, RBV, and warfarin.[27] Also, Peterson et al.[28] evaluate the potential interaction between RBV and warfarin in a 63-year-old man under treatment with long-term warfarin and RBV. A decrease in INR was observed 12 weeks after the initiation of treatment.

RBV may increase the hepatotoxicity of lamivudine[29] and zidovudine may enhance the risk of hematological toxic effects of RBV, specially, and anemia.[29–31] The mechanism of interaction between RBV and zidovudine is competitive inhibition of intracellular phosphorylation of zidovudine by RBV.[32] The interaction between RBV and abacavir can be associated with competitive inhibition in metabolic pathways,[33] but this interaction is not significant.[34] Mitochondrial toxicity and severe metabolic acidosis syndrome are life-threatening adverse reactions associated with concomitant use of RBV and didanosine that can manifest with symptoms, including pancreatitis, hepatic steatosis, and lactic acidosis.[35–38] Inosine monophosphate dehydrogenase (IMPDH) is a key enzyme in metabolism of azathioprine (AZA) which RBV inhibit this enzyme and enhance the risk of myelotoxicity (i.e., anemia, thrombocytopenia) of AZA.[39] Interaction between RBV and telaprevir was described by Gutierrez-Valencia et al.[40,41] which may enhance the risk of hematological toxicity by increasing the blood levels of RBV. The mechanism of action of this interaction is inhibition of the proximal tubule transport of RBV by telaprevir.

The significant drug interaction may occur between alpha and beta antagonists with sofosbuvir/RBV regimen during HCV therapy that close monitoring is required.[42] The study conducted by Ramanathan et al.[43] has not demonstrated a pharmacokinetic interaction between tenofovir and RBV. The details of RBV drug interactions are shown in Table 1.

3 | CHLOROQUINE

Chloroquine, a 4-aminoquinolone derivative, is used in the prophylaxis and treatment of uncomplicated malaria. It is also effective in systemic lupus erythematosus and rheumatoid arthritis.[44–46] The serious side effects associated with chloroquine are retinopathy, ototoxicity, and myopathy.[47–50] Chloroquine can inhibit organic anion transporting polypeptide 1A2 that the inhibition of this transporter is associated with retinopathy.[51] Chloroquine can induce psoriasis in patient as exfoliative erythroderma and pustular psoriasis.[52] The National Health Commission of the People's Republic of China for tentative treatment of COVID-19 (version 6) recommends chloroquine for the treatment of COVID-19 at doses of 500 mg oral twice daily for 10 days that may shorten the recovery period and improve pulmonary complication findings in imaging.[53] In patients with CrCl <10 ml/min, the recommended dose of chloroquine is 50% normal dose.[16,53,54] Chloroquine is completely absorbed after oral administration and it is distributed widely in tissues that include kidney, liver, lung and spleen.[54] About 60% of chloroquine is bound to plasma proteins. It is metabolized by CYP2C8 and CYP3A4 enzymes in the liver and converted into active metabolites (desethylchloroquine and bisdesethylchloroquine).[54,55] The mechanism of action of chloroquine is inhibition of the polymerization of heme which heme accumulate as toxic agent in the parasite.[54]

The concomitant administration of chloroquine and paracetamol can increase significantly C_{max} of paracetamol and should be used cautiously.[56] The absorption of chloroquine may decrease by antacids and their administration should be separated by at least 4 h to reduce the risk of drug interaction.[57,58] A controlled study was performed by Ette et al.[59] for analysis of interaction between cimetidine and chloroquine. The results showed that cimetidine may decrease the metabolism of chloroquine and increase its volume of distribution. The study conducted by Ette et al.[60] showed no significant pharmacokinetic interaction between ranitidine and chloroquine. Therefore, ranitidine is the H_2 blocker of choice for ulcer patients receiving chloroquine. Several clinical studies indicate that chloroquine may increase the metformin-induced cell apoptosis and significantly enhance the metformin-induced inhibition of cancer

TABLE 1 The details of RBV drug interactions

Interacting drugs	The effect of RBV on ADME of other agent	The effect of other agent on ADME of RBV	Consequence	Risk for DDIs	References
Antiviral (anti-HIV)					
Didanosine	Mitochondrial toxicity by inhibition of inosine−5′-mono-phosphate ↑ intracellular inosine monophosphate pool	—	↑ serum concentration of the active metabolite(s) of didanosine ↑ risk of pancreatitis, hepatitis, hepatic steatosis, myopathy, neuropathy, lipodystrophy, or lactic acidosis Avoid combination if possible or close monitoring	X	35–38
Stavudine	RBV reduces phosphorylation of stavudine Severe mitochondrial toxicity	—	↑ risk of lactic acidosis, pancreatitis, and hepatic steatosis Avoid combination if possible	—	37
Zidovudine	RBV Inhibits the intracellular phosphorylation of zidovudine	—	Zidovudine may inhibit hematopoiesis and bone marrow response ↑ hematological side effect of RBV (anemia) Clinical significance Unknown	D	29–32
Telaprevir	—	inhibition of the proximal tubule transport of RBV	↑ plasma creatinine and plasma level of RBV ↑ risk of hematological toxicity No significant interaction	No significant	40,41
Lamivudine	Unknown mechanism	—	RBV may increase the hepatotoxicity of lamivudine Monitor hepatic enzymes (AST and ALT)	—	29
Abacavir	Competitive inhibition of phosphorylation	—	↓ antiviral potency of pegylated interferon plus RBV regimen RBV increases the toxicity of abacavir	No significant interaction	33
Immunosuppressive drug					
AZA	Inhibition of IMPDH by RBV Interferes with AZA metabolism and increase 6-methylthioinosine metabolite	—	↑ serum concentration of active metabolite(s) of AZA ↑ risk of myelotoxicity (i.e., anemia, thrombocytopenia) of AZA Avoid combination if possible; close monitoring required due to potential for increased hematologic toxicities	D	39
Vitamin K antagonists					
Warfarin	Unknown mechanism	—	↓ anticoagulant effect of warfarin	C	27,28

Abbreviations: AZA, azathioprine; IMPDH, inosine monophosphate dehydrogenase; RBV, ribavirin.

cell proliferation.[61–63] Chloroquine may increase the risk of hypoglycemic effect of antidiabetic agents.[64] Chloroquine may reduce the plasma concentration of methotrexate by 20%,[65] but there is no significant pharmacokinetic interaction between chloroquine and methotrexate. Pukrittayakamee et al.[66] studied the potential interaction between primaquine and chloroquine in 16 healthy volunteers. Based on the results, chloroquine may increase the serum concentration of primaquine and enhance the risk of QT prolongation. Chloroquine may increase the mean plasma concentration of penicillamine by 34%.[67] Chloroquine may reduce the plasma concentration of levothyroxine by increasing the catabolism and worsen the control of hypothyroidism.[68] Chloroquine may reduce the bioavailability and serum concentration of praziquantel by 50 may decrease by non-competitive inhibition of its metabolism by chloroquine.[69] Acute dystonic reaction was reported in a 30-year-old woman under treatment with chloroquine and metronidazole.[70] The pharmacokinetic study do not exhibit drug interaction between chloroquine and azithromycin.[71] Chloroquine may reduce the therapeutic effect of agalsidase Alfa and Beta.[72]

Chloroquine may reduce the bioavailability of ampicillin by decreasing the rate of gastric emptying and enhancement of bowel motility.[73] The co-administration of chloroquine and cyclosporine for malaria prophylaxis or rheumatoid arthritis may elevate cyclosporine levels.[74–76] Ciprofloxacin is a fluoroquinolone antibiotic with broad antibacterial activity which concomitant use of it with chloroquine may decrease its plasma concentration to below the minimum inhibitory concentration.[77,78] Patients should be cautioned regarding the concomitant use of chloroquine with tamoxifen because it increases

the risk of retinopathy.[79] The interaction between chloroquine and other QT prolonging agents such as antipsychotic drugs, cisapride, dronedarone, fluoxetine, tricyclic antidepressants, citalopram, escitalopram, amiodarone, mefloquine and beta blocker (sotalol) has been life threatening, leading to QT prolongation and ventricular arrhythmias.[80–82] Chloroquine can antagonize the antiepileptic effect of carbamazepine.[81] Chloroquine may inhibit the metabolism of metoprolol by the inhibition of CYP2D6.[83] An interaction between chloroquine and methylene blue was reported by Rengelshausen and co-workers.[84] No pharmacokinetic interaction is observed between chloroquine and imipramine.[85] There is no pharmacokinetic interaction between chloroquine with sulfadoxine and pyrimethamine.[86] Activated charcoal can reduce plasma level of chloroquine by 99% after 5 min.[87] Interaction between indinavir and chloroquine can be enhanced the antimalarial effect of chloroquine against chloroquine-resistant line and chloroquine-sensitive line P. chabaudi.[88] There is no clinically significant interaction between tafenoquine and chloroquine.[89] The details of chloroquine drug interactions are summarized in Table 2.

4 | LOPINAVIR/RITONAVIR

Kaletra® approved in 2000 for widely used in combination with other antiretroviral compounds to treat HIV-1 in children 14 days of age and older, also in adults.[90] Lopinavir binds to the HIV-protease site of activity and prevents the formation of functional proteins required for viral pathogenesis, resulting in non-infectious and immature viruses.[91] Ritonavir inhibits lopinavir metabolism via CYP3A4 and boosts the plasma levels of lopinavir. Furthermore, when co-formulated with ritonavir that improves the bioavailability of lopinavir. So it can be said, the significant antiretroviral effects of Kaletra are due to lopinavir.[92] Kaletra binds to plasma proteins approximately 98%–99%, and elimination half-life after a single-dose administration is nearly 2–3 h. Kaletra is mainly eliminated with feces and is <2% in the urine.[90,93] Kaletra is classified as category C in pregnancy and only prescribed when the beneficial impacts of this on the fetus exceed from harmful effects.[90] The possible adverse effects of Kaletra are hyperglycemia (≤5%), abdominal pain (1%–11%), pancreatitis (≤2%), diarrhea (7%–28%), lipid elevation (3%–39%), nausea (5%–16%), and vomiting (adults 2%–7%; children 21%), and QT prolongation (≤2%). Kaletra could be recommended in high-risk patients (old patients or patients with underlying disorders) with COVID-19 as an adjunctive medication based on the evidence of in vitro studies. It was prescribed 400/100 mg twice daily for 14 days.[94,95] Nevertheless, recently the results of many studies in the administration of Kaletra in COVID-19 patients have been controversial. Such as the Coa et al. randomized controlled open-label trial at 199 hospitalized patients with COVID-19 (99 patients receiving Kaletra and 100 patients receiving standard care for 14 days) demonstrated that the use of Kaletra alone has not advantageous for clinical improvement in severe COVID-19.[96] A randomized controlled trial in patients with severe COVID-19 in Guangzhou, China, was performed to evaluate the efficacy and safety of Kaletra or Arbidol in comparison with the control group and showed the use of Kaletra or Arbidol as monotherapy may not improve clinical outcomes instead increases adverse effects in hospitalized patients. Accordingly, more extensive clinical trials may be required to estimate the efficacy of Kaletra in patients with severe COVID-19.[97,98] Ritonavir is a potent inhibitor of the CYP3A4 and moderate inhibitor of P-glycoprotein, CYP2D6, OTAP1B1, and OTAP1B3. Also, induced the hepatic enzyme's CYP1A2, CYP2B6, and UGT1A1. Lopinavir is inhibiting CYP3A4 and CYP2D6.[99,100] Thus, Kaletra will be many interactions with other groups of medications, and it is crucial to consider these interactions in pharmacotherapy. These interactions with details were described in Table 3.

5 | TOCILIZUMAB

Tocilizumab (Actemra®) is a recombinant humanized monoclonal antibody against the soluble and membrane receptors of IL-6. It mainly used to treatment of autoimmune diseases such as rheumatoid arthritis and polyarticular juvenile idiopathic arthritis.[117] The mechanism of action of TCZ is inhibition of IL-6 receptors, which stimulates regulatory B cells, and reduces the expression of inflammatory cytokines and chemokine genes. As a result, it increases the expression of synovial fluid proteins.[118] Elimination of TCZ depends on the serum concentration of the drug and is associated with the degree of IL-6 receptor saturation. The non-linear pathway is prominent at low serum concentrations. At high concentrations, after the receptors are completely saturated, the non-specific linear elimination pathway will predominate. Besides, higher sustained target saturation occurs with infused doses of 8 mg/kg every 4 weeks (compared with 4 mg/kg), which leads to a longer half-life and reduced elimination. Extended exposure to high concentrations of the drug may enhance the responses.[117,119,120] The volume of distribution of TCZ is restricted to serum compartment. Its elimination rate is relatively slow.[121] The efficacy of the intravenous and subcutaneous formulations of TCZ have been studied and appear to be similar.[117,118] Common adverse effects associated with the use of TCZ are gastrointestinal problems, and increased risk of infection. Also, transient neutropenia, elevated hepatic enzymes, and increased total and LDL cholesterol may occur in patients receiving TCZ.[117,122] Other side effects that happen frequently are hypertension and headaches.[123] TCZ should not use during pregnancy because adequate evidence is not available for this population. Animal studies display at over human doses (>100 folds) may enhance the inevitable abortion slightly. Analysis of retrospective global results demonstrates that women who have an exposure to this medication for a short time in the first trimester or before conception do not experience a notable risk of anomalies.[118,124] Studies show that IL-6 is one of the key inflammatory cytokines in the development of SARS-induced inflammation, which raises the insufficiency of alveolar blood-gas exchange and eventually leads to lung fibrosis and organ failure.[125,126] In a study performed on 21 patients with critical

TABLE 2 "QT-prolonging antidepressants such as citalopram, escitalopram, fluoxetine" is in a same group with other "OT-prolonging agent"

Interacting drugs	The effect of chloroquine on ADME of other agent	The effect of other agent on ADME of chloroquine	Consequence	Risk for DDIs	References
Paracetamol	Chloroquine can increase significantly C_{max} of paracetamol	—	↑ paracetamol plasma concentration Avoid co-administration	—	56
Antacids	—	The absorption of chloroquine is reduced by antacids	Should be separated by at least 4 h Administration should be separated by at least 4 h	D	57,58
Cimetidine	—	Cimetidine inhibits the metabolism and clearance of chloroquine	May increase the serum concentration of Chloroquine Consider ranitidine as an alternative or take cimetidine at least 2 h after chloroquine Consider another antiulcer medication ranitidine or take cimetidine at least 2 h after CQ	C	59
Antidiabetic agent	Chloroquine increases insulin sensitivity	—	May increase the risk of hypoglycemic effect of antidiabetic agents (severe hypoglycemia) Check blood sugar level and reduce daily dose of insulin	C	64
Immunosuppressive drug					
Methotrexate	Chloroquine may reduce the bioavailability of methotrexate	—	↓ maximum plasma levels of methotrexate about 20% and ↓ it's AUC about 28%	Not significant	65
Cyclosporine	↓ metabolism of cyclosporine by competitive inhibition (inhibition of P-gp activity by chloroquine)	—	↑ cyclosporine levels Monitor renal function weekly and cyclosporine levels for toxicity	D	74–76
Primaquine	Chloroquine may enhance the serum levels of primaquine	—	↑ risk of QT interval prolongation Caution with drugs that affect cardiac conduction	C	66
Penicillamine	Chloroquine increases the peak plasma levels of penicillamine about 34%	—	Severe hematologic and renal toxicity Monitor acute toxicity	—	67
Levothyroxine	—	Chloroquine may increase the catabolism of levothyroxine by enzymatic induction	Chloroquine may decrease the plasma concentration of levothyroxine Poorly controlled hypothyroidism Monitor TSH levels when beginning and discontinuing chloroquine	—	68
Praziquantel	—	Chloroquine may decrease the bioavailability of praziquantel	Chloroquine may reduce the serum concentration of praziquantel about 50% An increased dosage of PZQ should be considered	C	69
Agalsidase-alfa and agalsidase-beta	—	Chloroquine inhibits intracellular α-galactosidase activity	↓ therapeutic effect of agalsidase-alfa and agalsidase-beta Agalsidase α/β should not be used with chloroquine	X	72

(Continues)

TABLE 2 (Continued)

Interacting drugs	The effect of chloroquine on ADME of other agent	The effect of other agent on ADME of chloroquine	Consequence	Risk for DDIs	References
Antibiotics					
Metronidazole	Pharmacodynamic interaction	—	Metronidazole increase the risk of dystonic reaction of chloroquine	—	70
Ampicillin	Chloroquine may decrease the rate of gastric emptying and gut motility	—	↓ absorption, bioavailability and serum concentration of ampicillin	D	73
Ciprofloxacin	Chloroquine may increase urinary excretion of Ciprofloxacin	—	The concentration of ciprofloxacin may decrease to below the minimum inhibitory concentration for Plasmodium falciparum Avoid co-administration	—	77,78
Tamoxifen	Mechanism is unclear, although tamoxifen is a retinal toxin (additive effect with chloroquine)	—	Tamoxifen may enhance the retinopathy of chloroquine. Monitor retinopathy regularly.	C	79
QT-prolonging agent					
Amisulpride	Additive effect with QT prolongative agent	—	The concomitant use can increase the risk of QT-interval prolongation. Monitor electrolytes level and ECG regularly.	C	80–82
Domperidone				D	
Fexinidazole				X	
Haloperidol				C	
Ondansetron				C	
Pentamidine				C	
Pimozide				X	
Mefloquine				X	
QT-prolonging antidepressants such as citalopram, escitalopram, fluoxetine				C	
Carbamazepine	Chloroquine can antagonize the antiepileptic effects of carbamazepine.	—	Chloroquine decrease seizure threshold Increased dose of carbamazepine	—	81
Metoprolol	Chloroquine inhibits the metabolism of metoprolol	—	↑ the plasma level of metoprolol (AUC about 65% and peak plasma level 72%) Reduce daily dose of metoprolol	—	83
Methylene blue	—	Methylene blue may decrease the AUC of chloroquine (about 20%)	↓ the plasma level of chloroquine	—	84
Activated charcoal	—	The absorption of chloroquine may be diminished by activated charcoal	The effect of chloroquine may diminish in the presence of activated charcoal Avoid co-administration	—	87
Indinavir	—	Synergistic activity	Indinavir can be increased the antimalarial activity of chloroquine	—	88

TABLE 3 Kaletra drug interactions

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
HMG-CoA reductase inhibitors (statins)					
Atorvastatin	Atorvastatin is a CYP3A4 substrate and kaletra will increase the concentration by 5.9 times in the concomitant use	—	Avoid concurrent use or utilize alternative medicine. When the concomitant use is unavoidable, the dose of atorvastatin should not exceed 20 mg per day. Besides the signs of toxicity should be carefully evaluated	D	100,101
Lovastatin	Simultaneous use with Kaletra will increase plasma concentration and risk of toxicity	—	Contraindicated	X	100,102
Pravastatin	Kaletra can increase the plasma concentration of pravastatin to near 33% during concomitant use(due to inhibiting of OTAP1B1)	—	Use with caution	—	100,101
Rosuvastatin	Kaletra increases the effects of rosuvastatin by reduction in metabolism	—	Avoid concomitant use or utilize alternative medication	D	100,102
Simvastatin	The liver enzymes are inhibiting through Kaletra. Thus, systemic exposure of simvastatin and the risk of rhabdomyolysis increase	—	Contraindicated	X	100,103
Antimalarial agents					
Atovaqoune	The plasma concentration of Atovaqoune decreases to 74% during simultaneous use with Kaletra	—	Should be monitoring closely	C	100
Proguanil	The plasma level and AUC of proguanil reduces to 40% when concurrent use with Kaletra (due to inducing of CYP2C19 enzyme by Kaletra)	—			
Quinine	The plasma level of quinine increase when concomitant use with ritonavir and its dose should be decreased by 50%. On the other hand, lopinavir and quinine prolonged the QT interval	—	Contraindicated	X	100,104,105
PDE−5 inhibitors					
Sildenafil Tadalafil Vardenafil	Kaletra will increase the effect of these medications by affecting hepatic/intestinal enzyme CYP3A4 metabolism	—	Start as the lower dose when to use simultaneously. For example, the start dose of sildenafil should not be more than 25 mg in 48 h	D	102,106
Antifungal agents					
Posaconazole	Ritonavir increases plasma concentrations of Posaconazole by P-glycoprotein efflux transporter	Posaconazole can increase the level of Kaletra by affecting CYP3A4 metabolism	Should be used with caution	C	100,107
Voriconazole	Ritonavir reduces plasma levels of voriconazole by boosting metabolism	Voriconazole can raise the concentration of Kaletra by affecting CYP3A4 metabolism	Contraindicated	X	

(Continues)

TABLE 3 (Continued)

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
Eplerenone	Plasma level of eplerenone increases due to the effect of ritonavir on CYP3A4	—	Contraindicated	X	101
Calcium channel blockers					
Amlodipine	The effect of Amlodipine increases in concomitant use with Kaletra via interacting with CYP3A4	—	Should be used with caution	C	100,101,108
Non-dihydropyridine	All of them are metabolized by CYP3A4. So, the elevated serum concentration of CCBs through PIs may increase the risk of AV nodal blockade and PR prolongation	—	Avoid concomitant use or use by monitoring of CCB toxicity	D	
Digoxin	Ritonavir increases the level of digoxin about 29% via P-glycoprotein efflux transporter also by reducing renal and hepatic clearance	—	The effects of digoxin should be monitored carefully in concurrent use with Kaletra. Also, digoxin can prolong the PR interval in combination with PIs	D	100,101
Alfa 1 blockers					
Doxazosin Prazosin Terazosin	The systemic levels of these drugs increase in concurrent use with Kaletra as they are CYP3A4 substrates	—	The plasma level should be exactly titrated	—	99,101,108
Alfuzosin	The plasma level of Alfuzosin increases due to the effect of ritonavir on CYP3A4. Also, the QT interval will increase with both lopinavir and alfuzosin	Also, the QT interval will increase with both lopinavir and alfuzosin	Contraindicated	X	
Tamsulosin	Kaletra will increase levels of tamsulosin by affecting CYP3A4 and 2D6 metabolism	—			
Beta blockers					
Carvedilol Metoprolol	Ritonavir can increase the effect of these medications in concomitant use by affecting CYP2D6 metabolism. As a result, bradycardia and PR prolongation have been reported	—	Using atenolol instead of these medications is recommended.	—	99–101
Anti-arrhythmic medications					
Amiodarone Dronedarone Flecainide Ivabradine Propafenone Mexiletine	All of these drugs are substrates for hepatic enzymes (CYP3A4 and 2D6) metabolism. Their plasma levels are increased by the use of Kaletra concurrently. Thus, they may cause cardiac toxicity and many anomalies in the ECG, such as prolonged QT interval	—	Co-administration of these medications with Kaletra is contraindicated	X — — — — —	99–101,108
Anticoagulants					
Apixaban	Kaletra increases the effects of apixaban by affecting CYP3A4 metabolism	—	Avoid concomitant use or utilize alternative medication	D	99,101

(Continues)

TABLE 3 (Continued)

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
Dabigatran	Kaletra will increase the plasma concentration of dabigatran and edoxaban by P-glycoprotein efflux transporter	—	Although a recent case report illustrated that the safe administration of dabigatran with Kaletra by planning consumption to be 1 h apart, co-administration should be with caution	—	100,101,109
Edoxaban			Avoid concomitant use or utilize alternative medication.	D	101
Rivaroxaban	Kaletra will increase the levels of rivaroxaban via affecting CYP3A4 metabolism	—	This combination may increase the risk of bleeding. So, avoid concomitant use	X	99,101
Warfarin	Ritonavir decreases the metabolism of R-warfarin by inhibiting the CYP3 A4 enzyme. On the other hand, it increases the metabolism of warfarin due to the stimulation of CYP 2D9 and CYP 1A4 enzymes. In general, it will raise the need for warfarin by 2–3 folds	—	Accordingly, INR should be checked routinely during concurrent use with Kaletra	C	99,101,110
Antidiabetic agents					
Nateglinide	Kaletra decreases effects of nateglinide.	—	Should be monitoring closely.	—	99,111
Repaglinide	Kaletra will increase the effects of these medications by affecting CYP3A4 metabolism.	—	Should be used with caution.	C	
Saxagliptin			Limit the dose to 2.5 mg/day while co-administered by strong CYP3A4 inhibitors.	D	
Corticosteroids					
Budesonide (Nasal & Inhaler)	Kaletra increases the effect of these medications by affecting hepatic enzyme's metabolism. Thus, in concomitant use of corticosteroids with Kaletra may cause Cushing syndrome	—	Concurrent use does not suggest. Beclomethasone or Flunisolide could be replaced for these drugs	C	99,100,112
Fluticasone (Nasal)				X	
Triamcinolone				C	
Disulfiram	—	Disulfiram may enhance the toxicity of Kaletra through inhibition of aldehyde dehydrogenase	Contraindicated	X	106
Colchicine	The plasma level of Colchicine will be increased if used with Kaletra concurrently	—	This combination is contraindicated in cases with hepatic or renal impairment	D	99
Antipsychotic agents					
Lurasidone	Kaletra increases the effect of Lurasidone by affecting CYP3A4 metabolism	—	Co-administration of this drug and strong CYP3Aa inhibitors are contraindicated	X	106
Olanzapine	Kaletra will increase the effect of Olanzapine by affecting CYP3A4 metabolism	—	Should be used with caution	C	
Quetiapine	The plasma concentration of Quetiapine will increase when used concomitantly with ritonavir. Additionally, both Kaletra and Quetiapine are prolonging the QT interval	—	Its dose should be reduced to one sixth of the standard dose	D	

(Continues)

TABLE 3 (Continued)

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
Analgesics					
Buprenorphine	Kaletra may increase the serum level of Buprenorphine by affecting CYP3A4 metabolism	—	Should be monitored closely	C	100,106
Codeine	Kaletra decreases the serum concentration of Codeine by affecting CYP2D6 metabolism	—			99
Methadone	Due to the effect of Kaletra on liver enzymes, the AUC significantly decreased during concomitant use with Kaletra®. It also prolongs the QT interval	—			99,100,106
Oxycodone	The plasma concentration of oxycodone increases by 2–3 fold with Kaletra, by affecting CYP3A4 & 2D6 metabolisms	—	It should start with a low dose and monitor the effects of toxicity	D	99,100,113
Tramadol	The plasma level of tramadol increases with Kaletra because metabolized by CYP3A4	—	Should be monitoring closely	C	99
Anticonvulsants					
Carbamazepine	When used concomitantly with ritonavir compounds, carbamazepine may reach toxic levels	Carbamazepine decreases the level of Kaletra by affecting CYP3A4 metabolism	Accordingly, close monitoring and dose adjustment will be needed	D	100,106
Lamotrigine	The half-life of lamotrigine reduces in co-administration with Kaletra	—	Its dose should be increased by 50%	D	106
Phenytoin	—	Phenytoin will decrease the level of Kaletra to 33% by stimulation of hepatic enzymes (CYP3A4 & P-glycoprotein) metabolism	The dose of Kaletra should increase at the concurrent use	D	100
Valproate (Divalproex)	Kaletra may reduce the serum level of Divalproex	—	Should be monitoring closely	C	106
Antidepressants					
Bupropion	Kaletra decreases the serum concentration of bupropion to 57% by inducing CYP2B6 metabolism	—	Should be monitoring closely	C	99,106
Citalopram Escitalopram	Kaletra increases levels of citalopram & escitalopram by affecting CYP3A4 metabolism. So the risk of serotonin syndrome and QT prolongation increases	—	The monitoring of ECG recommended when using Kaletra concurrently. Also, the dose of these drugs should not exceed 20 mg daily for above 60 years	—	99,100
Fluoxetine	Ritonavir increases the effect of fluoxetine by affecting CYP2D6 metabolism	—	—	—	99,100

(Continues)

TABLE 3 (Continued)

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
Mirtazapine	Kaletra increases serum concentration of mirtazapine by affecting CYP3A4 metabolism	—	If concurrent use with Kaletra, administration of the minimum effective dose should be considered	C	106
Nefazodone	Nefazodone metabolized by CYP3A4. So, the plasma level and adverse effects of nefazodone may increase in using with Kaletra concurrently	—	As a result, toxic effects must be monitored closely. The maximum dose should be limited to 50–100 mg/day	D	106
Trazodone	Kaletra may increase the level of trazodone to 240% by inhibiting CYP3A4 metabolism	—	Using lower initial dose and monitoring CNS & cardiovascular effects should be considered when combined with Kaletra	D	99,106
Natural products					
Red yeast rice	Kaletra increases the effect of Red Yeast Rice by inhibiting CYP3A4 metabolism. As a result, it may increase the risk of rhabdomyolysis or myopathy and creatine kinase levels	—	Contraindicated	X	100
St John's Wort	—	St John's Wort will decrease the effect of Kaletra by affecting CYP3A4 metabolism and P-glycoprotein efflux transporter	Contraindicated	X	100,106
Sedative-hypnotics & anxiolytics					
Alprazolam	Kaletra will increase the effect of these medications by inhibiting CYP3A4 metabolism	—	Monitoring for increased toxic effects of alprazolam and starting to be careful prescribing if combined with Kaletra	D	106
Buspirone			It should be monitored closely for side effects	D	106
Midazolam			Contraindicated	X	106,114
Triazolam			Co-administration with PIs increases the hypnotic effects and psychomotor disorders. Therefore, this combination is contraindicated	X	106
Zolpidem			Should be monitoring closely	C	99
Salmeterol	Kaletra may increase the effect of salmeterol by inhibiting CYP3A4 metabolism	—	Simultaneous use contraindicated due to increased cardiac complications	X	99
Antibacterials					
Rifabutin	Ritonavir may increase the serum concentration of rifabutin by reducing metabolism	Furthermore, rifabutin may decrease the effect of Kaletra by affecting CYP3A4 metabolism	Should be dose modification and closely monitoring considered	D	100

(Continues)

TABLE 3 (Continued)

Interacting drugs	The effect of kaletra on ADME of other agent	The effect of other agent on ADME of kaletra	Consequence	Risk for DDIs	References
Rifampin	—	Rifampin may decrease the level of Kaletra by affecting CYP3A4 metabolism and P-glycoprotein efflux transporter. This combination may increase the risk of toxicity specifically may result in hepatocellular toxicity	Contraindicated	X	100
Ergotamine	Ritonavir increases level of ergotamine by decreasing CYP3A4 metabolism	—	Contraindicated	X	100
Dronabinol	Dronabinol is a CYP3A4 substrate and Kaletra may increase the level of dronabinol by inhibiting CYP3A4 metabolism	—	Should be monitoring closely	C	99
Antineoplastics					
Bortezomib	These medications are often CYP3A4, CYP2B6, and P-glycoprotein substrates. As a result, Kaletra may increase the plasma concentration of antineoplastic agents by inhibiting these hepatic enzyme's metabolism	—	—	C	99,115,116
Cyclophosphamide				C	
Docetaxel				D	
Doxorubicin				D	
Erlotinib				D	
Imatinib				C	
Irinotecan				X	
Sunitinib				D	
Vinblastine				D	
Vincristine				D	
Vinorelbine				C	

COVID-19, TCZ was combined at a dose of 400 mg intravenously with common drug regimens. Clinical data demonstrate that the symptoms, variations in CT-opacity, and hypoxemia rapidly improved after the TCZ administration. No side effects or lung infections reported during treatment. Accordingly, TCZ could be recommended as an effective medication for severe cases of COVID-19.[127] In vitro studies explain that TCZ inhibits the downregulation of CYP (CYP3A4, CYP2C9, CYP2C19, and CYP1A2) enzymes by IL-6, which may interact with medications that are a substrate for these enzymes. Therefore, when taken concomitantly with medicines that have a narrow therapeutic window such as warfarin, phenprocoumon, theophylline, cyclosporine, and phenytoin should be considered particular care. Also, due to the long half-life of TCZ, it may be required monitoring of these interactions for 1–2 months after discontinuation of TCZ.[117,128] One study reported three cases of mesenteric arterial thrombosis associated with the application of TCZ in patients who were under previous anticoagulant therapy. The use of TCZ may stimulate the metabolism of anticoagulants by reducing the inhibitory effects of IL-6 on CYP450 enzymes. Rivaroxaban is a substrate of CYP3A4 and P-glycoprotein, and warfarin is a substrate of the CYP2B6, CYP3A4, CYP2C19, and CYP2C9 enzymes which used simultaneously with TCZ reduces the plasma concentration of these anticoagulants. So, this can lead to thrombosis. P-glycoprotein restricts the absorption of dabigatran. Inhibition of IL-6 by TCZ, modifying P-glycoprotein function, thereby reducing the bioavailability of dabigatran etexilate. Accordingly, concurrent use with TCZ reduces the anticoagulant effects of dabigatran and helps to progress thrombosis.[129] Pharmaceutical interactions studies show that simvastatin plasma levels (substrate CYP3A4) decrease when administered concurrently with TCZ. In other words, 1 week after administration of 10 mg/kg single dose of TCZ, the AUC of simvastatin reduces by 57% (2.3-fold reduction).[121,130] The combination of TCZ with TNF-α inhibitors such as adalimumab, due to their synergistic effect on modulating the immune responses, concerns about serious infections and injection site reactions increases.[118,131] Also, a combination of omeprazole and TCZ decreases omeprazole AUC by increased CYP2C19 activity.[121] The details of TCZ drug interactions are summarized in Table 4.

TABLE 4 TCZ and RDV drug interactions

Tocilizumab					
Interacting drugs	**The effect of TCZ on ADME of other agent**	**The effect of other agent on ADME of TCZ**	**Consequence**	**Risk for DDIs**	**References**
Anticoagulants					
Dabigatran etexilate	TCZ may reduce the effects of these medications by affecting the CYP450 enzyme's metabolism and function of P-glycoprotein	—	This combination may increase the risk of thrombosis	—	117,129
Phenprocoumon				—	
Rivaroxaban				—	
Warfarin				—	
Simvastatin	TCZ decreases the concentration of simvastatin by affecting CYP3A4 metabolism	—	Should be used with caution	—	121,130
Theophylline	TCZ may reduce the effects of theophylline and phenytoin by affecting the CYP450 enzymes metabolism	—	Should be dose modification and closely monitoring considered	—	117,128
Phenytoin				—	
Cyclosporin	TCZ may reduce the effect of cyclosporin. Also, a combination of cyclosporin with TCZ increases the risk of infection	—	Should be dose adjustment and monitoring closely	—	
Omeprazole	TCZ reduces the concentration of omeprazole by affecting CYP2C19 metabolism	—	Should be used with caution	—	121
Adalimumab (Anti TNF-α agents)	Both of them increase risk of serious infection and immunosuppressive effects		Contraindicated	X	118,131

Remdesivir					
Interacting drugs	**The effect of RDV on ADME of other agent**	**The effect of other agent on ADME of RDV**	**Consequence**	**Risk for DDIs**	**References**
Rifampicin	Concomitant use may increase the risk of hepatotoxicity		Contraindicated	X	132
Methimazole	Unknown mechanism	—	Dose monitoring recommended in concurrent use	—	132
Immunosuppresive agents	RDV may affect the plasma level of these medications by an unknown mechanism	—	Monitoring levels of immunosuppressive medications suggested in concomitant use	—	133
Carbamazepine	—	Carbamazepine could decrease the levels of RDV significantly	This interaction not reported experimentally	—	134

Abbreviations: Risk for DDIs columns: X: Avoid Combination; D: Consider Therapy Modification; C: Monitor Therapy; —: Enough data are not available.

6 | REMDESIVIR

Remdesivir (by pharmaceutical code: GS-5734) is an antiviral medication. In 2014, the effects of RDV on Ebola virus was evaluated by Eastman et al.[135] in West Africa. RDV is a prodrug of nucleoside analogous that metabolized via intracellular anabolic kinase to active nucleoside triphosphate metabolite (GS-443902) in tissues.[94] It inhibits the activity of RNA polymerase and prevents duplication of virus in the infectious cycle.[94,136,137] In 2017, the antiviral effects of RDV on the SARS and MERS viruses were evaluated and show effective results against these viruses and other coronaviruses.[138] With the advent of COVID-19, hopes for the efficacy of RDV increased again. Some studies, such as Wang et al., have shown that the RDV has a notable effect on the restriction of viral infection in cultured cells in the laboratory.[13] Besides, in vitro and pre-clinical in-vivo animal models also support the effects of RDV against SARS-CoV-2.[135] RDV is produced as a lyophilized powder and is administered as an IV infusion over 30 min to achieve high concentrations of active intracellular metabolite.[94] Based on pharmacokinetic data, the plasma half-life of RDV prodrug is short ($t_{1/2}$ = 0.39 h) when prescribed at a dose of 100 mg/day by a loading dose of 200 mg for a maximum of 10 days in non-human primates. However, levels of intracellular triphosphate form remain in the human body for a longer time

($t_{1/2}$ = 20 h).[133,135] Data related to the elimination pathway of RDV and dose adjustment in patients with renal or hepatic impairment are not available.[94,133] Reported adverse effects of RDV in three patients in the United States include vomiting, rectal bleeding without other symptoms, nausea and gastroparesis. Also, these patients experience high levels of aminotransferase during 1–5 days after the initiation of RDV.[94] The most prominent side effect of RDV appears to increase liver enzymes (ALT & AST). For this reason, the evaluating level of liver enzymes before starting treatment with RDV is recommended. If the ALT level was more (>5 fold) than the normal upper limit, RDV must hold or not initiate. Additionally, RDV should not be used in glomerular filtration rate <30 ml/min.[132] Available information for RDV during pregnancy is inadequate. Only one randomized trial investigated the effects of RDV in six pregnant women during the Ebola epidemic and any side effects not reported.[139] So far, no contraindications have identified for this medication; except concurrent use with other proven hepatotoxic drugs such as rifampicin. Based on the rapid pharmacokinetics of distribution, metabolism, and excretion of RDV, the probability of clinical interactions seems low (dose monitoring recommended in concomitant use with methimazole).[132] No interaction found between immunosuppressants and RDV. Nevertheless, when using with RDV concomitantly monitoring levels of immunosuppressive medications suggested.[133] RDV at in vitro studies appears to be a substrate for CYP2C8, CYP2D6, and CYP3A4 enzymes. However, on in vivo conditions, the metabolism of RDV is following the action of hydrolase, which indicates that potential clinical interactions with inhibitors or inducers of CYP enzymes are unlikely. For example, the concurrent use of RDV with carbamazepine could decrease the levels of RDV significantly, whereas this interaction not reported experimentally. Moreover, according to the weak role of hepatic enzymes in RDV metabolism, the probability of this interaction will be much lower. In general, RDV drug interactions are not verified carefully. Accordingly, possible interactions may help to discover potential clinical drug interactions associated with RDV.[134] Generally, the evidence about the safety and efficacy of RDV in the treatment of COVID-19 is limited. Due to the ambiguous effects of RDV against COVID-19, it has not been obtained definitive approval from FDA. Only ordered for patients in clinical trials, emergency states, or compassionate use.[135,140,141] These interactions with details were described in Table 4.

7 | CONCLUSION

COVID-19 is currently a global and life-threatening issue and there is no FDA-approved vaccine for prevention of it. FDA approves emergency use of RDV for COVID-19. Based on the clinical data, pharmacotherapy including chloroquine, Kaletra, RBV, and TCZ is recommended for the treatment of COVID-19. Patients with underling disease have a higher risk for COVID-19 infection because often need to be treated with multiple medications. Polypharmacy may increase the risk of DDIs and decrease patient compliance. DDI may put the patient at risk for serious adverse effects and reduce safety and efficacy of treatment. Chloroquine and Kaletra are metabolized by CYP 450 enzymes. In conclusion, they have a higher potential for drug interaction with CYP 3A4 inducers or inhibitors. The interaction of chloroquine or Kaletra with other QT prolonging agents has been life threatening and it is necessary to monitor the plasma concentration of these drugs. The concomitant use of chloroquine and tamoxifen may enhance the risk of retinopathy. The induction of CYP enzymes by TCZ may reduce the effect of other drugs that are metabolized by these pathways. Concomitant use of TCZ and immunosuppressants such as cyclosporine and adalimumab is contraindicated because this interaction can increase the risk of infection. Drug interactions of each drug are described in details and tabulated for easy access. It will be useful to guide clinicians in drug selection, improve safety of treatment, and decrease the risk of adverse drug events.

DISCLOSURES

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

H.R. and M.N-V. devised the main conceptual ideas. F.P., S. P-A., and H.R. wrote the initial draft of the manuscript. H.R., F.P., and S.P-A. prepared the figures. M.N-V., T.E-M., and T.A-K. reviewed the manuscript and edited it critically for important intellectual content. M.N-V. supervised the study.

DATA AVAILABILITY STATEMENT

Not applicable.

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