
Universiteit
Leiden
The Netherlands

Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions

Elens, L.; Langman, L.J.; Hesselink, D.A.; Bergan, S.; Moes, D.J.A.R.; Molinaro, M.; ... ; Lemaitre, F.

Citation
Elens, L., Langman, L. J., Hesselink, D. A., Bergan, S., Moes, D. J. A. R., Molinaro, M., ... Lemaitre, F. (2020). Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. *Therapeutic Drug Monitoring*, *42*(3), 360-368. doi:10.1097/FTD.0000000000000761

Version:	Publisher's Version
License:	Creative Commons CC BY-NC-ND 4.0 license
Downloaded from:	https://hdl.handle.net/1887/3181918

Note: To cite this publication please use the final published version (if applicable).

Pharmacologic Treatment of Transplant Recipients Infected With SARS-CoV-2: Considerations Regarding Therapeutic Drug Monitoring and Drug–Drug Interactions

Laure Elens, PhD,† Loralie J. Langman, PhD,‡ Dennis A. Hesselink, MD, PhD,§¶ Stein Bergan, PhD,‖ Dirk Jan A.R. Moes, MD, PhD,** Mariadelfina Molinaro, MScBiol,†† Raman Venkataramanan, PhD,‡‡ and Florian Lemaitre, PhD§§¶¶*

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

Background: COVID-19 is a novel infectious disease caused by the severe acute respiratory distress (SARS)-coronavirus-2 (SARS-CoV-2). Several therapeutic options are currently emerging but none with universal consensus or proven efficacy. Solid organ transplant recipients are perceived to be at increased risk of severe COVID-19 because of their immunosuppressed conditions due to chronic use of immunosuppressive drugs (ISDs). It is therefore likely that solid organ transplant recipients will be treated with these experimental antivirals.

Methods: This article is not intended to provide a systematic literature review on investigational treatments tested against COVID-19; rather, the authors aim to provide recommendations for therapeutic drug monitoring of ISDs in transplant recipients infected with SARS-CoV-2 based on a review of existing data in the literature.

Results: Management of drug–drug interactions between investigational anti-SARS-CoV-2 drugs and immunosuppressants is a complex task for the clinician. Adequate immunosuppression is necessary to prevent graft rejection while, if critically ill, the patient may benefit from pharmacotherapeutic interventions directed at limiting SARS-CoV-2 viral replication. Maintaining ISD concentrations within the desired therapeutic range requires a highly individualized approach that is complicated by the pandemic context and lack of hindsight.

Conclusions: With this article, the authors inform the clinician about the potential interactions of experimental COVID-19 treatments with ISDs used in transplantation. Recommendations regarding therapeutic drug monitoring and dose adjustments in the context of COVID-19 are provided.

Key Words: COVID-19, SARS-CoV-2, drug interactions, transplant patients, therapeutic drug monitoring, experimental treatments, calcineurin inhibitors, mammalian target of rapamycin inhibitors, mycophenolic acid, tacrolimus, cyclosporin, sirolimus, everolimus, recommendations, immunocompromised, hydroxychloroquine, chloroquine, remdesivir, protease inhibitors, lopinavir, tocilizumab

(*Ther Drug Monit* 2020;42:360–368)

INTRODUCTION

In December 2019, a cluster of unexplained pneumonia cases was diagnosed in Wuhan, China. The causative agent was identified as a novel coronavirus, named Severe Acute Respiratory Syndrome (SARS) Corona Virus 2 (SARS-CoV-2). The associated disease has been named Corona VIrus Disease 2019 (COVID-19) and the outbreak is now considered a pandemic by the World Health Organization.

Solid organ transplant recipients are perceived to be at increased risk of severe COVID-19 because of their chronic immunosuppressed status because of the use of immunosuppressive drugs (ISDs). There is at present limited experience with the treatment of affected transplant recipients. The continuation and proper dose or target of ISD is still matter of debate.[1] Moreover, no proven effective therapeutic intervention other than supportive care is now available. The scale of the outbreak and the considerable severity of the disease in many cases have prompted several pharmacologic interventions. Laboratory research has identified more than 30 agents that may have potential efficacy against SARS-CoV-2.[2–4] Drugs that have been and are being tested in humans include (hydroxy)chloroquine, darunavir/cobicistat (DRV/COB) or DRV/ritonavir (DRV/r), favipiravir, interferon (IFN), lopinavir/r (LPV/r), ribavirin, remdesivir (manufactured by

Received for publication April 9, 2020; accepted April 13, 2020.

From the *Louvain Drug Research Institute (LDRI), Integrated Pharmacometrics, Pharmacogenomics and Pharmacokinetics (PMGK), Université catholique de Louvain (UCLouvain), Brussels, Belgium; †Institut de Recherche Expérimentale et Clinique (IREC), Louvain Center for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain (UCLouvain), Brussels, Belgium; ‡Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota; §Division of Nephrology and Transplantation, Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; ¶Rotterdam Transplant Group; ‖Department of Pharmacology, Oslo University Hospital, Oslo, Norway; **Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands; ††Clinical and Experimental Pharmacokinetics Lab, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ‡‡School of Pharmacy and Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; §§Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)—UMR_S 1085, Rennes, France; and ¶¶INSERM, Centre d'Investigation Clinique, CIC 1414, Rennes, France.

The authors declare no conflict of interest.

Correspondence: Laure Elens, PhD, Université catholique de Louvain (UCLouvain), Louvain Drug Research Institute (LDRI), Integrated Pharmacometrics, pharmacogenomics and pharmacokinetics (PMGK), Avenue Emmanuelle Mounier 72 B01.02, 1200 Bruxelles, Belgium (e-mail: laure.elens@uclouvain.be).

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

Gilead, Foster City, CA), and tocilizumab (manufactured by Roche, Basel, Switzerland, and Chugai, Tokyo, Japan), the last 2 being available for compassionate use or for clinical trials). There is no consensus on which pharmacotherapeutic strategy to follow. Several professional societies have developed recommendations and guidelines to help clinicians with these investigational and off-label medicinal products.[5]

Transplant patients are treated life-long with ISD whose pharmacodynamics (PD) and pharmacokinetics (PK) can be affected by these antivirals. Furthermore, COVID-19 patients may exhibit features of systemic hyperinflammation (designated as "cytokine storm"), which can be associated with so-called "phenoconversion," a phenomenon whereby extensive metabolizers transiently exhibit drug metabolizing enzyme activity at a comparable level as that of poor metabolizers.[6,7] Commonly, ISDs are characterized by a narrow therapeutic index and wide PK variability, requiring close monitoring of the blood concentrations. Also, the metabolic pathways involved in clearance of ISDs make these drugs extremely susceptible for drug–drug interactions (DDIs). Calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORi) are primarily metabolized by cytochrome P450 (CYP) 3A, their oral bioavailability is poor, erratic and also limited by the fact that they are substrate for P-glycoprotein (P-gp or ABCB1).[8] Mycophenolate mofetil (MMF) is a prodrug that is converted in vivo into mycophenolic acid (MPA). The metabolism of MPA mainly involves glucuronidation by the uridine 5′-diphosphate-glucuronosyltransferase (UGT) enzyme superfamily.[9] MPA is subjected to entero-hepatic recirculation, which extends its terminal half-life. Hepatic excretion of MPA glucuronide (MPAG) is driven by uptake from the portal vein through OATP1B3 and, to a lesser extent, OATP1B1. MPAG is then excreted in the bile actively through ABCC2.[10]

The purpose of this article is to inform the clinician about the potential interaction of drugs against coronavirus with IS drug therapy used in transplantation (summarized in Table 1). In addition, recommendations regarding therapeutic drug monitoring (TDM) in the context of COVID-19 are made.

(HYDROXY)CHLOROQUINE

Mode of Action and Pharmacokinetics

Chloroquine is an aminoquinolone derivative first developed in the 1940s that has been used for the prophylaxis and treatment of malaria. It acts by inhibiting the action of heme polymerase in malarial trophozoites, thereby blocking the formation of hemozoin from heme which is released by the digestion of hemoglobin.[11] Chloroquine and its derivative, hydroxychloroquine, have since then been repurposed for the treatment of a number of other conditions including viral infections, systemic lupus erythematosus, and rheumatoid arthritis. Hydroxychloroquine is an analogue of chloroquine in which one of the N-ethyl substituents of chloroquine is β-hydroxylated. Generally, hydroxychloroquine is preferred when high doses are required because of its lower level of toxicity and higher therapeutic index.[12] Moreover, hydroxychloroquine (EC50 = 0.72 μmoles/L) was found to be more potent than chloroquine (EC50 = 5.47 μmoles/L) in vitro against SARS-CoV-2.[13] A recent clinical trial in France reported that the use of hydroxychloroquine was associated with a significant reduction of SARS-CoV-2 viral load.[14] However, this study has limitations, including bias in its design that renders the interpretation of these results delicate. Other preliminary results obtained from patients are conflicting.[15] The relevance of (hydroxy)chloroquine for treating COVID-19 is now being evaluated in larger, more controlled, multicenter randomized clinical trials.[16]

Hydroxychloroquine and chloroquine are well absorbed with a bioavailability of 70%–80%. Both are ~50% bound to plasma proteins and widely distributed in tissues such as liver, spleen, kidney, and lung, resulting in an extremely large volume of distribution (~800 L/kg).[17] Chloroquine is metabolized in the liver by cytochrome P450 (CYP)2C8 and CYP3A4 and to a lesser extent by CYP3A5 and CYP2D6.[18] Hydroxychloroquine is N-de-alkylated by CYP3A4 to the active metabolite desethylhydroxychloroquine, as well as the inactive metabolites desethylchloroquine and bidesethylchloroquine.[19] Around 50% and 20% is eliminated unchanged in urine for chloroquine and hydroxychloroquine, respectively. Both drugs have long and variable terminal elimination half-lives (approximately 40–60 days).[18,20,21]

Dosing and Mode of Administration in COVID-19

In patients with COVID-19, chloroquine has been administered orally at a dose of 300 mg (500 mg for chloroquine phosphate) for adults, 2 times/day for a maximal duration of 10 days. Hydroxychloroquine therapy is started at a loading dose of 400 mg b.i.d. on day 1 and then lowered to 200 mg b.i.d. (or t.i.d. in some particularly compromised patients) from day 2 onward. Given the long half-life of hydroxychloroquine, a loading dose is necessary to shorten the time to reach target concentrations. The duration of hydroxychloroquine therapy varies across countries (from 5 to up to 20 days).

Interactions With ISD

(Hydroxy)chloroquine, CNIs [both cyclosporin (CsA) and tacrolimus (Tac)], and mTORi can all cause prolongation of the QT interval.[22–24] Even if unpredictable, in theory, the concurrent use of 2 drugs that cause QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and, although rare, sudden death. This is the reason why (hydroxy)chloroquine should be administered with great caution in patients on CNIs and mTORi. In addition, even if no cases have been reported yet, it might be expected that everolimus (EVR) would increase the (hydroxy)chloroquine concentrations given its potential effect on CYP3A (as determined by its interaction with midazolam) and possibly potentiate its effect on the QT interval.[25] Vice versa, (hydroxy)chloroquine may increase CsA concentrations by inhibiting its metabolism through direct inhibition of the CYP3A4 enzyme.[26–30]

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1. Potential Importance of Drug–Drug Interactions Between Immunosuppressive Drugs and Investigational COVID-19 Treatments and Recommendations With Grading in Brackets

	(Hydroxy)chloroquine	Lopinavir/Ritonavir (Kaletra)	Darunavir (Prezista)	Darunavir/Cobicistat (Rezolsta)	Favipiravir, Remdesivir, Tocilizumab (Investigational)
Tac					
Risk level	Moderate—major	Major	Major	Major	No information available
Outcome	QT-interval prolongation.	Increased Tac concentrations; may result in an increased risk of Tac toxicity	Increased Tac concentrations; may result in an increased risk of Tac toxicity	Increased Tac concentrations; may result in an increased risk of Tac toxicity	
Our recommendations	QT interval monitoring (required)	Consider a Tac dosing regimen of 0.5–1 mg once weekly and close TDM (highly recommended)	If RTV boosted: Consider a Tac dosing regimen of 0.5–1 mg once weekly and close TDM. If unboosted: Close TDM (highly recommended)	Consider a Tac dosing regimen of 0.5–1 mg once weekly and close TDM (highly recommended)	—
CsA					
Risk level	Moderate	Moderate-major	Major	Major	No information available
Outcome	Increase the concentration of CsA may result in an increased risk of CsA toxicity	Increased CsA concentrations; may result in an increased risk of CsA toxicity	Increased CsA concentrations; may result in an increased risk of CsA toxicity	Increased CsA concentrations; may result in an increased risk of CsA toxicity	
Our recommendations	QT interval monitoring (required)	Consider a CsA dosing regimen of 25 mg every 1–2 days and close TDM. ! possible delay in Tmax (highly recommended)	If RTV boosted: Consider a CsA dosing regimen of 25 mg every 1–2 days and close TDM. Possible delay in tmax if unboosted: Close TDM (highly recommended)	Consider a CsA dosing regimen of 25 mg every 1–2 days and close TDM. possible delay in tmax (highly recommended)	
EVR					
Risk level	None—low	Major	Major	Major	No information available
Outcome		Increased EVR concentrations; may result in an increased risk of EVR toxicity	Increased EVR concentrations; may result in an increased risk of EVR toxicity	Increased EVR concentrations; may result in an increased risk of EVR toxicity	
Our recommendations	QT interval monitoring (required)	Consider weekly dosing interval and close TDM (highly recommended)	If RTV boosted: Consider weekly dosing interval and close TDM. If unboosted: Close TDM (highly recommended)	Consider weekly dosing interval and close TDM (highly recommended)	
SRL					
Risk level	None reported	Major	Major	Major	No information available
Outcome		Increased SRL concentrations; may result in an increased risk of SRL toxicity	Increased SRL concentrations; may result in an increased risk of SRL toxicity	Increased SRL concentrations; may result in an increased risk of SRL toxicity	
Our recommendations	QT interval monitoring (required)	Consider weekly dosing interval and close TDM (highly recommended)	If RTV boosted: Consider weekly dosing interval and close TDM. If unboosted: Close TDM (highly recommended)	Consider weekly dosing interval and close TDM (highly recommended)	
MPA					
Risk level	None	None	None	None	No information available
Our recommendations		Close TDM (suggested)	Close TDM (suggested)	Close TDM (suggested)	
Prednisolone					
Risk level	None	Major	Moderate—major	Moderate—major	No information available
Outcome		Increased steroid concentrations and decreased plasma cortisol; may result in development of Cushing syndrome	Increased prednisolone concentrations	Increased prednisolone concentrations	
Our recommendations	QT interval monitoring (recommended)	Monitor patient (in)tolerance and biochemical parameters for dosage adjustment (suggested)	Monitor patient (in)tolerance and biochemical parameters for dosage adjustment (suggested)	Monitor patient (in)tolerance and biochemical parameters for dosage adjustment (suggested)	

Tac, tacrolimus; CsA, ciclosporin; EVR, everolimus; SRL, sirolimus.[98–100]

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

Recommendations

When coadministration of (hydroxy)chloroquine together with CNI and/or mTORi is considered.

1. QT interval monitoring is strongly recommended.
2. Prompt medical attention should be paid to symptoms that could indicate the occurrence of cardiac arrhythmia such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope. As these symptoms can occur as a result of COVID-19, they might be wrongly attributed to the viral infection itself instead of drug-associated cardiac toxicity. Consequently, we recommend that these drugs should only be administered when cardiac monitoring is available.
3. CsA blood concentrations should be closely monitored as an increase in CsA exposure is expected and the dose may need to be decreased.
4. The same may be anticipated with Tac, EVR, and sirolimus (SRL) due to a potential competitive inhibition through CYP3A4/5.
5. Analytical solutions exist for monitoring (hydroxy)chloroquine drug concentrations.[31–33] Regarding efficacy, interpretation of such TDM data is difficult because of the lack of data on target concentrations, timing of measurement, and drug adjustment strategy in the context of COVID-19 treatment. Avoiding toxic exposure is even more important considering the long half-life of (hydroxy) chloroquine; hence, monitoring (hydroxy)chloroquine concentrations is suggested for this purpose. However, so far, there are no data to identify the threshold concentration for increased toxicity. Based on in vitro data and physiologically based PK modeling, it has been recently suggested that a plasma concentration of 0.1 mcg/mL (0.3–0.5 mcg/mL in whole blood) might be sufficient to generate a lung concentration far above the EC50 for SARS-CoV-2.[13]

(Hydroxy)chloroquine, on the other hand, does not appear to influence the concentrations of other ISD to a clinically relevant degree. The usual TDM strategy for these agents is advocated whenever (hydroxy)chloroquine is prescribed.

PROTEASE INHIBITORS

Mode of Action and Pharmacokinetics

Protease inhibitors (PIs) act by selectively inhibiting the HIV-1 protease, thereby preventing the post-translational processing of viral gag and gag-pol polyprotein products into smaller functional proteins, an essential step for the maturation of new virions. LPV also has inhibitory activity on the proteinase of SARS-CoV-1 in vitro,[34,35] an enzyme which is key in CoV polyprotein processing. Inhibition of SARS-CoV-1 has been reported at peak and trough serum LPV concentrations.[36] LPV also blocks a post entry step in the MERS-CoV replication cycle, conferring this drug a promising potential agent for COVID-19.[37] Recent results based on an in silico approach showed that several HIV inhibitors such as LPV, ritonavir (RTV), and saquinavir strongly interact with the active site of COVID-19 proteinase,[38] and researchers in China reported that DRV inhibited COVID-19 infection in vitro,[39] validating the use of PI against COVID-19. However, these results are controversial as Cao et al[40] recently demonstrated no benefit with LPV/r treatment beyond standard care in COVID-19–positive patients.

Currently, PIs are generally prescribed along with a PK booster, either RTV or, more recently, COB. RTV blocks CYP3A-mediated metabolism of LPV thereby prolonging its exposure. Cotreatment with boosted PI regimens is thus inherently challenging because of their complex spectrum of DDIs. DRV, LPV and their boosters, either RTV or COB, inhibit (and sometimes induce) various cytochromes and transporters, thereby affecting also other therapies like ISD. Indeed, DRV is a substrate for CYP3A, ABCB1, ABCC2, OATP1A2, OATP1B1, and OATP1B3,[41] with the potential to inhibit CYP3A4, ABBC2, OATP1B1, and OATP1B3. LPV is metabolized primarily through CYP3A hepatic metabolism and transported by ABCB1 and ABCB2. LPV has been reported to induce its own metabolism (ie, CYP3A) but also other CYP (eg, CYP2B6) through PXR activation[42] and may be a potent inhibitor of ABCC2.[43,44] Meanwhile, the boosters, RTV and COB, exert slightly different effects: both are capable of inhibiting CYP3A, OATP1B1, and OATP1B3, while RTV may also induce other CYP isoforms.[45–47] RTV also increases the biotransformation of some drugs metabolized by glucuronidation catalyzed by UGT, although the clinical relevance of this effect is not clear. Through their inhibition on ABCB1 and CYP3A, it is expected that those drugs will influence CNIs and mTORi PK while by their inhibitor activity on OATP and ABCC2 as well as induction of UGT1A9 and UGT2B7 through PXR activation,[48] they can interfere with MPA entero-hepatic recirculation and exposure.[49]

Dosing and Mode of Administration in COVID-19

The recommendation for the use of LPV/r is 400 mg/100 mg b.i.d. for adults for 10–21 days. DRV at a dose of 800/100 mg o.d. (DRV/r), 800/150 mg o.d. (DRV/COB), or 600/100 mg b.i.d. (DRV/r) for 5 consecutive days is considered as a possible alternative in some countries but is not endorsed by the manufacturer because of a lack of evidence to support use of darunavir-based treatments for COVID-19.[50]

Interaction With ISDs

In contrast to the PD interaction discussed above between (hydroxy)chloroquine and ISDs, the PK interaction between PIs and ISD is well documented.

Calcineurin Inhibitors and mTORi

Clinical studies have shown that dramatically lower daily doses and prolonged dosing intervals for CNIs are necessary in HIV-infected patients using unboosted PIs.[51,52] Moreover, in patients on RTV-boosted PIs, even more drastic ISD dose reductions (up to 120-fold) were necessary to achieve therapeutic through concentrations of Tac, CsA, and SRL.[51–53] Regarding Tac, in a case series of HIV-positive liver transplant recipients, it was concluded that when used in combination with LPV/r, the usual requirement of Tac was less than 1 mg/wk with normal liver function.[54]

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

Alternatively, using tailored "microdosing" has been shown to be effective in maintaining adequate Tac blood concentrations when coadministered with boosted PIs.[55] Adding unboosted PIs to CsA, significantly decreased the dosing requirements to 57 mg per day on average, and increased the dosing interval to 21 hours rather than the usual 12 hours.[53] For PI regimens with RTV, the CsA dose requirement was decreased further to 25 mg per day, with an even greater dosing interval of 33 hours on average.[53] Quantitatively, it has been estimated that CNI half-life is prolonged 5- to 20-fold because of the systemic inhibition of CYP3A and ABCB1, resulting in dosing regimens of 0.5–1 mg once weekly for Tac and 25 mg every 1–2 days for CsA in kidney and liver transplant recipients. All in all, these data strongly suggest that initiation of a boosted-PI therapy in CNI-treated transplant recipients with no dosage adjustment will lead to extremely high and persistent CNI concentrations and overimmunosuppression and corresponding toxicity. Indeed, there are many reports of nephrotoxicity and neurotoxicity as a result of overexposure to CNIs because the CNI dose was not reduced beforehand.[51] Even when anticipated, pre-emptive dose reductions were often too small.[56,57]

DDIs with COVID-19 PI-based treatment can modify not only ISD concentrations but also the PK profile of the drug. Given the large interindividual variability of ISD PKs, predicting exposure during drug interaction appears very hazardous. The main concern when using PI with CNIs is not only an increase in area under the concentration versus time curve (AUC) but also the potential reshaping of the PK profile of the IS agent resulting in a more flattened curve.[58] The underlying assumption for CNI monitoring using a single sample is that this correlates with the AUC, which is considered the best measure of drug exposure. The total drug exposure is indeed increased, as reflected by the higher AUC, but the curve is smoothed. Consequently, some patients may exhibit a flat PK profile and the anticipated relationship, for example, the C0/AUC ratio, may therefore change.[59] For CsA, it was demonstrated that the concentration at 4 hours correlated better with AUC than C_0 or C_2. The best single timepoint to monitor thus appears to have shifted from 2 hours (usual case) to at least 4 hours when coadministered with a PI. Similar trends as with CNIs were seen with transplant subjects on SRL[53] and EVR. Drastic reduction in SRL dosing has been reported in patients on HIV PIs.[56,57]

Recommendations for CNIs/mTORi

When considering boosted PI therapy, we recommend that ISD dose be significantly reduced and also dosing intervals should be increased to once a week or twice a week.

1. For Tac and CsA, data suggest that dosing regimens of 0.5–1 mg once weekly for Tac and 25 mg every 1–2 days for CsA are appropriate when coadministered with boosted PI regimens. Solutions of microdosing might also be useful if further dose reduction is needed (eg, tacrolimus granules for oral suspension 0.2 mg, 2 or 3 times per week).[60]
2. In addition to drastic dose reduction, TDM should be conducted from day 1 of the coadministration thereafter, on a daily basis until stable (target) concentrations are reached.
3. Characterizing the full exposure (AUC) could be a valuable option when a PK reshaping is suspected as was proposed for Tac in the recent IATDMCT consensus on Tac TDM.[61]
4. In the intensive care unit (ICU), the presence of a central arterial line facilitates multiple sampling to determine the AUC. However, the measures of isolation of COVID-19 patients in the hospital might restrict the entry to their rooms. Limited sampling strategy (LSS) with Bayesian estimation of AUC can be proposed as an alternative.[62–64] Noninvasive sampling technique such as dried blood spot analysis is another possibility but seems more appropriate for transplant patients with mild complaints who are in quarantine at home.[62,63,65,66]
   - For Tac, a target $AUC_{0–12h}$ of 100–190 ng·h/mL ng.h/mL for twice daily regimen and $AUC_{0–24h}$ of 180–350 ng·h/mL for once daily is proposed. These values correspond to a C_0 target between 5 and 10 ng/mL.[61,67] If lower/higher C_0 are aimed for, the AUC target should be lowered/increased accordingly.[61]
   - For CsA, in kidney transplant, it is recommended to target a $AUC_{0–12}$ of 3250 ng·h/mL at 1 year after transplantation.[68,69] Alternatively, exposure during the first 4 hours ($AUC_{0–4h}$) is normally a reliable estimate of total drug exposure.[69–71] However, caution should be taken for $AUC_{0–4}$ interpretation because of the possible reshaping of the PK curves observed with PIs coadministration (see above).
5. For other ISDs, the pharmacokinetics of which is greatly influenced by CYP activity, such as mTORi an important shift in drug exposure with boosted PIs is expected although less-well defined than for CNIs. Because of the long half-life of SRL (62 hours in stable renal transplant recipients) and EVR (~30 hours), it is recommended that the dosing frequency of SRL and EVR when coadministered with CYP3A4 inhibitors should be extended to achieve target trough concentrations.[72] However, for practical reasons, greater dose reductions with weekly dosing intervals appear more practical when PI and mTORi are coadministered. With LPV/r coadministration, it has been suggested to decrease the SRL maintenance dose to 0.2 mg/wk[57]

Mycophenolate Mofetil

As mentioned above, LPV is a potent inhibitor of ABCC2[43] and the boosters have the potential to reduce the hepatic uptake mediated through OATP inhibition. The net effect would thus be a decrease of MPAG biliary excretion and consequently, decreasing entero-hepatic-recirculation, lowering MPA exposure. This information is of importance as the hepatic uptake of MPAG and subsequent biliary excretion is a prerequisite for MPA entero-hepatic recirculation, which is estimated to account for up to 61% of total MPA exposure.[73] However, no data are currently available to support an important PK interaction between boosted PI regimens and MPA.

Recommendations for MMF

In cardiothoracic transplant recipients, it is recommended to consider stopping MMF while the patient is admitted

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

with severe/critical illness (with close monitoring for rejection).[74] Similar decisions should be considered in critically ill COVID-19–positive patients other than cardiac transplant recipients. This decision is reinforced by the fact that it seems that MMF reduces the seroresponse of transplanted patients, as observed during the H1N1 pandemic.[75,76] However, if it is decided that MMF should be continued, we recommend caution and MPA monitoring with possible MMF dosage adjustment in COVID-19–positive transplant patients. There is difficulty in defining which time point to measure for MPA monitoring. MPA C_0 cannot be considered as a good surrogate for total exposure but is the most practical if a single time point is to be used.[77] Ideally, $AUC_{0–12h}$ should be obtained from samples collected during the whole dose interval as it is considered as the most robust PK marker. However, the blood collection schedules for $AUC_{0–12h}$ measurement are not practically sustainable in a crisis situation where access to COVID-19 dedicated rooms is restricted because of a high risk of medical staff infection. Alternatively, LSS have been proposed with at least 3 time points, commonly within 3 hours after drug intake. Further TDM strategies recommend to include an additional time point later than 4 hours to catch the second peak due to enterohepatic recycling (preferably around 8 or 9 hours after MMF dosing).[77] Extending the LSS this way could also compensate for the increased uncertainty of PK models which have not been validated in patients with this combination of interfering drugs.

Glucocorticoids

Glucocorticoid clearance has been reported to be significantly reduced in patients on RTV-boosted PIs resulting in higher serum concentrations and side effects.[78,79]

Recommendations for Glucocorticoids

Since glucocorticoid concentrations are not routinely monitored, doses are mostly adjusted based on patient (in) tolerance and biochemical parameters. Besides, the CDC recommends to avoid high-dose glucocorticoids in COVID-19–positive patients because of the potential for prolonging viral replication as was observed in MERS-CoV patients[80,81] and because, at present, clinical evidence does not support glucocorticoid treatment for SARS-CoV-2-mediated lung injury.[82] It is, however, recommended that, for patients who regularly use glucocorticoids for chronic diseases, a conservative but cautious attitude should be adopted with preservation or slight reduction of the usual dose.[83]

Remdesivir

Mode of Action and Pharmacokinetics

Remdesivir is a novel adenosine analogue initially developed to treat Ebola virus disease.[84] After conversion to its corresponding triphosphate metabolite, remdesivir incorporates into nascent viral RNA chains, thereby inhibiting the RNA polymerase, which results in premature termination of the RNA transcription. Remdesivir is neither licensed nor approved yet by the FDA and EMA and has not been demonstrated to be safe or effective for any use. However, in vitro results suggest that remdesivir EC_{90} against COVID-19 is compatible with concentrations observed in vivo.[85] At present, 9 clinical trials are registered to evaluate the safety and antiviral activity of remdesivir in patients with COVID-19 (www.clinicaltrial.gov accessed April 1, 2020). Enrollment in clinical trials is normally the primary way to access remdesivir. Emergency treatment and compassionate use requests are considered only when enrollment in a clinical trial is not a feasible option. However, to streamline the emergency access process, remdesivir's manufacturer Gilead (Foster City) is transitioning from individual compassionate use requests to expanded access programs in order to respond to the COVID-19 outbreak.

PK data indicate that the half-life of remdesivir is short while the nucleoside triphosphate metabolite has a longer half-life of approximately 20 hours in humans. As this drug is relatively new, data regarding the route of elimination are not available.

Dosing and Mode of Administration in COVID-19

Remdesivir is administered intravenously at a dose of 100 mg per day with a loading dose of 200 mg for a maximum of 10 days.

Interaction With IS Drugs and Recommendations

No clinical interaction is expected between any of the above-mentioned ISD and remdesivir. Nevertheless, we recommend caution and suggest close monitoring of ISD concentrations during coadministration with remdesivir because of the lack of knowledge and studies evaluating the safety of coadministration. A strict TDM of ISD is therefore proposed especially since these drugs may be used in severe and rapidly evolving situations.

TOCILIZUMAB

Mode of Action and Pharmacokinetics

There is evidence that the SARS-CoV-2 infection is associated with a cytokine storm triggered by overactivated immune system. What happens at the cellular level is a high production of GM-CSF and others inflammatory cytokines by $CD4^+$ T cells with further activation of $CD14^+$ $CD16^+$ monocytes to produce interleukin-6 (IL-6). It was postulated that blocking GM-CSF or IL-6 receptor would potentially reduce immunopathology caused by SARS-CoV-2.[86] Tocilizumab is a humanized IgG1k monoclonal antibody, which can specifically bind soluble or membrane type IL-6 receptors. To date, it has been widely used in the treatment of autoimmune diseases such as rheumatoid arthritis[87] and large vessel vasculitis.[88] Since in most of severe SARS-CoV-2–infected patients significantly higher serum levels of inflammatory mediators are found than in stable ones, a beneficial impact of this drug has been postulated in severe cases. A multicenter, randomized, controlled clinical trial is under way to examine the efficacy and safety of tocilizumab in patients with COVID-19 (ChiCTR2000029765), administered as compassionate use off label for this new pathology.

After intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. Tocilizumab has a nonlinear pharmacokinetic profile; the half-life and the clearance are concentration-dependent.[89] At steady-state in

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

patients with rheumatoid arthritis, the apparent half-life is up to 11 days for 4 mg/kg and up to 13 days for 8 mg/kg every 4 weeks.[89] In vitro studies in hepatocytes have shown that tocilizumab blocks the downregulation of CYP450 (mainly CYP3A4) that is caused by IL6.[90] The relevance of this finding is still unclear as this IL6 downregulation has only been demonstrated at very high concentrations in vitro. However, it would be prudent to consider this interaction for ISD that are metabolized by CYP3A4 due to altered proinflammatory cytokines concentrations in severe COVID-19 cases (cytokine storm).

Dosing and Mode of Administration in COVID-19

The recommended posology for the treatment of cytokine release syndrome (CRS) is 8 mg/kg (in 1 hour i.v. infusion) up to 800 mg per dose.

Interaction With IS Drugs and Recommendations

As for remdesivir, to date, no data on DDI with ISD are available. However, drastic reduction of IL levels can influence CYP3A activity by reverting the phenoconversion. We recommend thus caution and careful ISD TDM when tocilizumab is administered. Because of the long half-life of tocilizumab, it has been suggested that monitoring of this interaction may be necessary for months after tocilizumab is discontinued.[91]

ISD MONITORING IN ICU-ADMITTED COVID-19 PATIENTS

The most severe infections with COVID-19 may result in patient admission to the ICU. Adjusting drug dose in critical care patients is a real challenge as these patients often present with organ dysfunction, lower serum albumin, high volume of distribution, inflammation and vasopressors use; resulting in potential alterations in distribution and metabolism. These factors can lead to changes in drug PK, which is of particular relevance for narrow therapeutic index drugs such as ISD.

The management of the ISD treatment is a complex issue. On the one hand, complete or partial (with only glucocorticoids monotherapy) treatment, discontinuation of other ISD might help infection recovery and has been proposed by some authors in kidney transplant patients with severe pneumonia including case reports on COVID-19 infections,[92–94] but exposed patients to graft rejection. In case of severe pneumonia, discontinuation of MPA has also been proposed as a first step due to its low viral safety profile, while mTORi can lead to interstitial pneumonia which cannot be easily distinguished from SARS-CoV-2–induced lung disease.[95] On the other hand, optimizing ISD exposure during this highly variable phase requires pharmacological considerations and a close monitoring of the patients. Practical details to consider are the drug formulation (eg, administration of medications through feeding tubes can be opted). However, this may lead to reduced absorption of Tac, in particular when the drug is administered with enteral nutrition. Moreover, diarrhea and other changes in gastrointestinal motility can lead to an increase in Tac exposure.[96] Also, the inflammatory state of the patient is important to consider. It has been demonstrated that inflammatory cytokines may downregulate cytochrome P450 expression (phenoconversion).[97] Even without any consideration for DDI with COVID-19 treatment, a particular look should be given to biological inflammation parameters prompting clinicians to decrease dosages of ISDs particularly for substrates of CYP3A4/5 (ie, Tac, CsA, EVR, SRL) and, if the drugs are administered through feeding tubes, whether they are administered apart from enteral nutrition. It also appears reasonable to target the lowest acceptable ISD blood exposure (eg, up to a trough concentration of 3–5 ng/mL or preferably an AUC_{0-12} of 75–100 ng.h/mL for Tac) when monitoring patients during COVID-19 infections. In the ICU setting, due to the large PK variability observed in critical care patients, the frequent and close monitoring of ISD drugs is mandatory to optimize patient's management.

CONCLUSIONS

Management of COVID-19 patients is an intricate issue that is complicated in frail populations such as immunocompromised patients. Not only is this population more at risk of infection but, as described throughout this manuscript, management of ISD therapy is a real challenge. Little evidence exists to guide clinicians. Initiation of COVID-19 pharmacotherapy can throw the established ISD response off balance either from a PD or from a PK point of view. We provide here some considerations and recommendations aiming at helping clinicians in managing investigational COVID-19 treatments in ISD-treated transplant patients. Caution and careful monitoring should be the rule when experimental COVID-19 treatments are being initiated in ISD-treated transplant recipients irrespective of the drug combination. These considerations are made in the context of hospitalized transplant recipient suffering from COVID-19. For those patients who are in quarantine at home, dried blood spot–based home blood collection and TDM appear as appropriate solutions to avoid potential exposure of these patients during travel and at clinics, doctor's, or phlebotomist's offices. Finally, an additional attention and extension of careful TDM measures should be envisaged when stopping drugs coadministration because of possible reversion of the phenotypic consequences.

ACKNOWLEDGMENTS

The initiative for this paper was taken by the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

REFERENCES

1. *tts. [web site]*. Available at: https://tts.org/txjcovid19.
2. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther.* 2020;14:58–60.
3. Li H, Zhou Y, Zhang M, et al. Updated approaches against SARS-CoV-2. *Antimicrob Agents Chemother.* 2020. doi: 10.1128/AAC.00483-20.
4. *Danish Medicine Agency. [web site]*. Available at: https://laegemiddelstyrelsen.dk/da/nyheder/temaer/ny-coronavirus-covid-19/~/media/5B83D25935DF43A38FF823E24604AC36.ashx.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

5. *Center for Disease Control. [web site]*. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html.
6. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. *J Clin Invest.* 2020. doi: 10.1172/JCI137647.
7. Suzuki Y, Muraya N, Fujioka T, et al. Factors involved in phenoconversion of CYP3A using 4beta-hydroxycholesterol in stable kidney transplant recipients. *Pharmacol Rep.* 2019;71:276–281.
8. Elens L, Hesselink DA, van Schaik RH, et al. Pharmacogenetics in kidney transplantation: recent updates and potential clinical applications. *Mol Diagn Ther.* 2012;16:331–345.
9. Benjanuwattra J, Pruksakorn D, Koonrungsesomboon N. Mycophenolic acid and its pharmacokinetic drug-drug interactions in humans: review of the evidence and clinical implications. *J Clin Pharmacol.* 2020;60:295–311.
10. Hesselink DA, van Hest RM, Mathot RA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. *Am J Transpl.* 2005;5:987–994.
11. Kumar S, Guha M, Choubey V, et al. Antimalarial drugs inhibiting hemozoin (beta-hematin) formation: a mechanistic update. *Life Sci.* 2007;80:813–828.
12. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 2020;6:16.
13. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis.* 2020. doi: 10.1093/cid/ciaa237.
14. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label nonrandomized clinical trial. *Int J Antimicrob Agents* 2020;105949. doi: 10.1016/j.ijantimicag.2020.105949.
15. Chen Z, Hu J, Zhang Z, et al. *Efficacy of Hydroxychloroquine in Patients with COVID-19: Results of a Randomized Clinical Trial 2020:2020.2003.2022.20040758*. doi.org/10.1101/2020.03.22.20040758.
16. Clinicaltrial.gov. [web site]. Available at: https://clinicaltrials.gov/. Accessed April 7, 2020.
17. Furst DE. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. *Lupus.* 1996;5(suppl 1):S11–S15.
18. Kim KA, Park JY, Lee JS, et al. Cytochrome P450 2C8 and CYP3A4/5 are involved in chloroquine metabolism in human liver microsomes. *Arch Pharm Res.* 2003;26:631–637.
19. Lim HS, Im JS, Cho JY, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by Plasmodium vivax. *Antimicrob Agents Chemother.* 2009;53:1468–1475.
20. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine. Focus on recent advancements. *Clin Pharmacokinet.* 1996;31:257–274.
21. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* 2020;16:155–166.
22. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol.* 2006;44:173–175.
23. Ikitimur B, Cosansu K, Karadag B, et al. Long-Term impact of different immunosuppressive drugs on QT and PR intervals in renal transplant patients. *Ann Noninvasive Electrocardiol.* 2015;20:426–432.
24. White NJ. Cardiotoxicity of antimalarial drugs. *Lancet Infect Dis.* 2007;7:549–558.
25. Urva S, Bouillaud E, Delaney R, et al. A phase I study evaluating the effect of everolimus on the pharmacokinetics of midazolam in healthy subjects. *J Clin Pharmacol.* 2013;53:444–450.
26. Finielz P, Gendoo Z, Chuet C, et al. Interaction between cyclosporin and chloroquine. *Nephron.* 1993;65:333.
27. Nampoory MR, Nessim J, Gupta RK, et al. Drug interaction of chloroquine with ciclosporin. *Nephron.* 1992;62:108–109.
28. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singap Med J.* 1991;32:189–190.
29. Sarzi-Puttini P, D'Ingianna E, Fumagalli M, et al. An open, randomized comparison study of cyclosporine A, cyclosporine A + methotrexate and cyclosporine A + hydroxychloroquine in the treatment of early severe rheumatoid arthritis. *Rheumatol Int.* 2005;25:15–22.
30. Salaffi F, Carotti M, Cervini C. Combination therapy of cyclosporine A with methotrexate or hydroxychloroquine in refractory rheumatoid arthritis. *Scand J Rheumatol.* 1996;25:16–23.
31. Soichot M, Megarbane B, Houze P, et al. Development, validation and clinical application of a LC-MS/MS method for the simultaneous quantification of hydroxychloroquine and its active metabolites in human whole blood. *J Pharm Biomed Anal.* 2014;100:131–137.
32. Kaewkhao K, Chotivanich K, Winterberg M, et al. High sensitivity methods to quantify chloroquine and its metabolite in human blood samples using LC-MS/MS. *Bioanalysis.* 2019;11:333–347.
33. Morita S, Takahashi T, Yoshida Y, et al. Population pharmacokinetics of hydroxychloroquine in Japanese patients with cutaneous or systemic lupus erythematosus. *Ther Drug Monit.* 2016;38:259–267.
34. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol.* 2004;31:69–75.
35. Zhang XW, Yap YL. Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. *Bioorg Med Chem.* 2004;12:2517–2521.
36. Hurst M, Faulds D. Lopinavir. *Drugs.* 2000;60:1371–1379.
37. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother.* 2014;58:4875–4884.
38. Ortega JT, Serrano ML, Pujol FH, et al. Unrevealing sequence and structural features of novel coronavirus using in silico approaches: the main protease as molecular target. *EXCLI J.* 2020;19:400–409.
39. *News: Abidol and Darunavir Can Effectively Inhibit Coronavirus. [web site].* Available at: http://www.sd.chinanews.com/2/2020/0205/70145.html.
40. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med.* 2020.doi: 10.1056/NEJMoa2001282.
41. Konig SK, Herzog M, Theile D, et al. Impact of drug transporters on cellular resistance towards saquinavir and darunavir. *J Antimicrob Chemother.* 2010;65:2319–2328.
42. Svard J, Spiers JP, Mulcahy F, et al. Nuclear receptor-mediated induction of CYP450 by antiretrovirals: functional consequences of NR1I2 (PXR) polymorphisms and differential prevalence in whites and sub-Saharan Africans. *J Acquir Immune Defic Syndr.* 2010;55:536–549.
43. Holmstock N, Oorts M, Snoeys J, et al. MRP2 inhibition by HIV protease inhibitors in rat and human hepatocytes: a quantitative confocal microscopy study. *Drug Metab Dispos.* 2018;46:697–703.
44. Qazi NA, Morlese JF, Pozniak AL. Lopinavir/ritonavir (ABT-378/r). *Expert Opin Pharmacother.* 2002;3:315–327.
45. Lepist EI, Phan TK, Roy A, et al. Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, in vitro. *Antimicrob Agents Chemother.* 2012;56:5409–5413.
46. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet.* 1998;35:275–291.
47. Larson KB, Wang K, Delille C, et al. Pharmacokinetic enhancers in HIV therapeutics. *Clin Pharmacokinet.* 2014;53:865–872.
48. Hu DG, Meech R, McKinnon RA, et al. Transcriptional regulation of human UDP-glucuronosyltransferase genes. *Drug Metab Rev.* 2014;46:421–458.
49. Cattaneo D, Cossu MV, Rizzardini G. Pharmacokinetic drug evaluation of ritonavir (versus cobicistat) as adjunctive therapy in the treatment of HIV. *Expert Opin Drug Metab Toxicol.* 2019;15:927–935.
50. *Johnson & Johnson. [web site]*. Available at: https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus.
51. van Maarseveen EM, Rogers CC, Trofe-Clark J, et al. Drug-drug interactions between antiretroviral and immunosuppressive agents in HIV-infected patients after solid organ transplantation: a review. *AIDS Patient Care STDS.* 2012;26:568–581.
52. Marfo K, Greenstein S. Antiretroviral and immunosuppressive drug-drug interactions in human immunodeficiency virus-infected liver and kidney transplant recipients. *Transpl Proc.* 2009;41:3796–3799.
53. Frassetto LA, Browne M, Cheng A, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transpl.* 2007;7:2816–2820.
54. Jain AB, Venkataramanan R, Eghtesad B, et al. Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl.* 2003;9:954–960.
55. Bickel M, Anadol E, Vogel M, et al. Daily dosing of tacrolimus in patients treated with HIV-1 therapy containing a ritonavir-boosted

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/drug-monitoring by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 09/02/2022

protease inhibitor or raltegravir. *J Antimicrob Chemother.* 2010;65:999–1004.
56. Jain AK, Venkataramanan R, Fridell JA, et al. Nelfinavir, a protease inhibitor, increases sirolimus levels in a liver transplantation patient: a case report. *Liver Transpl.* 2002;8:838–840.
57. Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: an AIDS Malignancy Consortium Study. *J Acquir Immune Defic Syndr.* 2012;59:447–454.
58. Frassetto LA, Tan-Tam CC, Barin B, et al. Best single time point correlations with AUC for cyclosporine and tacrolimus in HIV-infected kidney and liver transplant recipients. *Transplantation.* 2014; 97:702–707.
59. Frassetto L, Baluom M, Jacobsen W, et al. Cyclosporine pharmacokinetics and dosing modifications in human immunodeficiency virus-infected liver and kidney transplant recipients. *Transplantation.* 2005; 80:13–17.
60. AstellasPharma Ldt. *Modigraf 0.2mg Granules for Oral suspension, summary of Product Characteristics (SmPC) [web site] 27 Sep 2019*.
61. Brunet M, van Gelder T, Asberg A, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. *Ther Drug Monit.* 2019;41:261–307.
62. Benkali K, Rostaing L, Premaud A, et al. Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in renal transplant recipients on a new once-daily formulation. *Clin Pharmacokinet.* 2010; 49:683–692.
63. Vethe NT, Gustavsen MT, Midtvedt K, et al. Tacrolimus can Be reliably measured with volumetric absorptive capillary microsampling throughout the dose interval in renal transplant recipients. *Ther Drug Monit.* 2019;41:607–614.
64. Leger F, Debord J, Le Meur Y, et al. Maximum a posteriori Bayesian estimation of oral cyclosporin pharmacokinetics in patients with stable renal transplants. *Clin Pharmacokinet.* 2002;41:71–80.
65. Monchaud C, Rousseau A, Leger F, et al. Limited sampling strategies using Bayesian estimation or multilinear regression for cyclosporin AUC(0-12) monitoring in cardiac transplant recipients over the first year post-transplantation. *Eur J Clin Pharmacol.* 2003;58:813–820.
66. Velghe S, De Troyer R, Stove C. Dried blood spots in therapeutic drug monitoring and toxicology. *Expert Opin Drug Metab Toxicol.* 2018;14: 1–3.
67. Scholten EM, Cremers SC, Schoemaker RC, et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipients. *Kidney Int.* 2005;67:2440–2447.
68. Press RR, Ploeger BA, den Hartigh J, et al. Explaining variability in ciclosporin exposure in adult kidney transplant recipients. *Eur J Clin Pharmacol.* 2010;66:579–590.
69. Cremers SC, Scholten EM, Schoemaker RC, et al. A compartmental pharmacokinetic model of cyclosporin and its predictive performance after Bayesian estimation in kidney and simultaneous pancreas-kidney transplant recipients. *Nephrol Dial Transpl.* 2003;18:1201–1208.
70. Johnston A, David OJ, Cooney GF. Pharmacokinetic validation of neoral absorption profiling. *Transpl Proc.* 2000;32:53S–56S.
71. Vester U, Kranz B, Offner G, et al. Absorption phase cyclosporine (C(2h)) monitoring in the first weeks after pediatric renal transplantation. *Pediatr Nephrol.* 2004;19:1273–1277.
72. Napoli KL, Kahan BD. Routine clinical monitoring of sirolimus (rapamycin) whole-blood concentrations by HPLC with ultraviolet detection. *Clin Chem.* 1996;42:1943–1948.
73. van Gelder T, Klupp J, Barten MJ, et al. Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. *Ther Drug Monit.* 2001;23:119–128.
74. *ISHLT. [web site]*. Available at: https://community.ishlt.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=f3c82518-b813-161b-698d-84992da8f4e3.
75. Mulley WR, Visvanathan K, Hurt AC, et al. Mycophenolate and lower graft function reduce the seroresponse of kidney transplant recipients to pandemic H1N1 vaccination. *Kidney Int.* 2012;82:212–219.
76. Resende MR, Husain S, Gubbay J, et al. Low seroconversion after one dose of AS03-adjuvanted H1N1 pandemic influenza vaccine in solid-organ transplant recipients. *Can J Infect Dis Med Microbiol.* 2013;24:e7–e10.
77. Tett SE, Saint-Marcoux F, Staatz CE, et al. Mycophenolate, clinical pharmacokinetics, formulations, and methods for assessing drug exposure. *Transpl Rev (Orlando).* 2011;25:47–57.
78. Wood BR, Lacy JM, Johnston C, et al. Adrenal insufficiency as a result of ritonavir and exogenous steroid exposure: report of 6 cases and recommendation for management. *J Int Assoc Provid AIDS Care.* 2015;14:300–305.
79. Busse KH, Formentini E, Alfaro RM, et al. Influence of antiretroviral drugs on the pharmacokinetics of prednisolone in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2008;48:561–566.
80. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet.* 2015;386:995–1007.
81. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med.* 2018;197:757–767.
82. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395: 473–475.
83. Shang L, Zhao J, Hu Y, et al. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet.* 2020;395:683–684.
84. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.* 2016;531:381–385.
85. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–271.
86. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506.
87. Kaneko Y, Kato M, Tanaka Y, et al. Tocilizumab discontinuation after attaining remission in patients with rheumatoid arthritis who were treated with tocilizumab alone or in combination with methotrexate: results from a prospective randomised controlled study (the second year of the SURPRISE study). *Ann Rheum Dis.* 2018;77:1268–1275.
88. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med.* 2017;377:317–328.
89. *Tocilizumab FDA Label. [web site]*. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf.
90. Long TJ, Cosgrove PA, Dunn RT II, et al. Modeling therapeutic antibody-small molecule drug-drug interactions using a three-dimensional perfusable human liver coculture platform. *Drug Metab Dispos.* 2016;44:1940–1948.
91. Sheppard M, Laskou F, Stapleton PP, et al. Tocilizumab (actemra). *Hum Vaccin Immunother.* 2017;13:1972–1988.
92. Tu GW, Ju MJ, Zheng YJ, et al. An interdisciplinary approach for renal transplant recipients with severe pneumonia: a single ICU experience. *Intensive Care Med.* 2014;40:914–915.
93. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transpl.* 2020. doi: 10.1111/ajt.15869.
94. Guillen E, Pineiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? *Am J Transpl.* 2020. doi: 10.1111/ajt.15874.
95. Ventura-Aguiar P, Campistol JM, Diekmann F. Safety of mTOR inhibitors in adult solid organ transplantation. *Expert Opin Drug Saf.* 2016; 15:303–319.
96. Tielemans MM, van Boekel GAJ, van Gelder T, et al. Immunosuppressive drugs and the gastrointestinal tract in renal transplant patients. *Transpl Rev (Orlando).* 2019;33:55–63.
97. Harvey RD, Morgan ET. Cancer, inflammation, and therapy: effects on cytochrome p450-mediated drug metabolism and implications for novel immunotherapeutic agents. *Clin Pharmacol Ther.* 2014;96:449–457.
98. *Drugs.com. [web site]*. Available at: https://www.drugs.com/interaction/.
99. *IBM Micromedex. [web site]*. Available at: https://www.micromedexsolutions.com/.
100. *Up to Date. [web site]*. Available at: https://www.uptodate.com/drug-interactions.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.