DRUG INTERACTION IN KIDNEY TRANSPLANT PATIENTS AND COVID-19 DRUG THERAPY

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DRUG–DRUG INTERACTIONS AND SIDE EFFECTS

- The suggested drug regimens for the treatment of COVID-19 have several drug–drug interactions and adverse drug reactions regarding immunosuppressive medications, which are mentioned in Table. These points are discussed in more detail below.

Drugs	Pharmacologic Category	Mechanism of Action	Dosage Regimen in COVID-19	References
Lopinavir/Ritonavir	Antiretroviral agent	Lopinavir is an HIV-1 protease inhibitor; ritonavir increases the half-life of lopinavir via inhibiting cytochrome P450	400 mg/100 mg twice daily for 7–14 days	39,40
Chloroquine/ Hydroxychloroquine	Antimalarial (aminoquinoline)	Chloroquine inhibits quinine reductase, an essential enzyme for biosynthesis of sialic acid, which is necessary for virus fusion with host cell	Chloroquine: 400 mg daily for 10–14 days Hydroxychloroquine: 500 mg twice daily for 10 days or 200 mg 3 times daily for 10 days	30,31,121
Umifenovir	Antiviral agent	Hemagglutinin inhibitor, which inhibits virus membrane fusion with host cell	200 mg every 12 hours for 10 days	65,66
Ribavirin	Antiviral agent	Inhibits protein synthesis via blocking IMPDH during replication of virus	1200–2000 mg daily divided into twice daily for 5 days	52,54,55
Remdesivir	Antiviral agent	Interferes with RNA polymerase	200 mg IV stat and then 100 mg daily for 9 days	58,64
Interferon	Interferons	Increases phagocyte activity of macrophages and augments cytotoxicity of lymphocytes for viral cells	5 million units twice daily via atomic nebulization or SQ administration	70,75,76
Tocilizumab	Antirheumatic/IL-6 receptor antagonist	Antagonist of intracellular IL-6 receptor	400 mg IV infusion stat	84

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IMPDH, inosine monophosphate dehydrogenase; IV, intravenous; IL, interleukin.

- If hydroxychloroquine is used in combination with lopinavir/ritonavir, a loading dose of 200 mg twice daily should be administered on the first day, then hydroxychloroquine should be discontinued and lopinavir/ritonavir initiated. An increase in liver enzymes, particularly when used concurrently with hepatotoxic drugs, gastrointestinal upset, and hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6P) deficiency are important

- This drug can cause QT prolongation, too. So, prior to initiating this medication, the risk factors for QT prolongation, including hypomagnesemia, hypokalemia, and cardiomyopathy, should be evaluated and eliminated if possible. This adverse effect can also occur when chloroquine or hydroxychloroquine is used in combination with lopinavir/ritonavir, another drug used for the management of COVID-19, or some other QTc-prolonging medications, including antipsychotics (eg, pimozide) or cardiac medications (eg, digoxin). Occasional headaches, dizziness, loss of appetite, and maculopathy (in long-term use) are other adverse effects of this drug.

- Individually, both hydroxychloroquine and azithromycin can cause disturbances in the cardiac conduction pathway leading to prolongation of the QT interval and predisposing to cardiac arrhythmias. Several studies of patients hospitalized with COVID-19 have raised concerns over QT interval prolongation from chloroquine/ hydroxychloroquine alone or in combination with azithromycin [63,64]. Both calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, and mammalian target of rapamycin inhibitors (mTORs), such as sirolimus and everolimus, can also cause QT interval prolongation

- Another potential adverse effect of hydroxychloroquine in SOT patients is myelosuppression, although this would be unlikely to occur in the setting of short-term treatment of COVID-19. Regarding drug-drug interactions, chloroquine and hydroxychloroquine are moderate inhibitors of the cytochrome P450-2D6 pathway. There have been reports of SOT recipients who experienced a threefold increase in serum cyclosporine concentrations following initiation of chloroquine

- Therefore, the cyclosporine level should be monitored periodically and the dose may be decreased if necessary. Removal of the drug by hemodialysis is negligible. It is suggested that 50% of the usual dose should be administered in patients with a glomerular filtration rate (GFR) <10 mL/min, but 100% of the usual dose is recommended for patients on continuous renal replacement therapy (CRRT).

LOPINAVIR/RITONAVIR

- Although some studies have reported positive effects of this drug on COVID-19, a recently published article questioned its efficacy. Based on limited studies, using lopinavir as monotherapy or in combination with umifenovir (Arbidol®), ribavirin, or interferon could help in the management of patients with COVID-19; however, a clinical trial did not demonstrate any superiority of lopinavir monotherapy over standard care supportive therapy. Therefore, further evaluations are required regarding its efficacy and safety.

- So far, few studies have been conducted regarding the use of this drug in liver and kidney transplant patients, but if it is administered to this population, its adverse effects and interactions with immunosuppressants and other medications used in transplant patients, such as fluoroquinolones for the treatment of Gram-negative infections, should be considered.

- PIs are known to cause impaired glucose tolerance, hepatotoxicity, and QT and PR interval prolongation. The potential for PI-related QT interval prolongation is highly relevant for any SOT patient on azithromycin-hydroxychloroquine, CNIs, or mTORs. PIs and their boosting agents are potent modulators of the hepatic cytochrome P450-3A4 pathway, leading to altered metabolism of critical medications in SOT recipients .

- PI-mediated inhibition of the P450-3A4 pathway can lead to significant reductions in glucocorticoid clearance. By the same mechanism, administration of PIs to SOT recipients on CNIs and mTORs can lead to elevations in immunosuppressive medications with narrow therapeutic indices. In order to avoid the dangerous side effects associated with elevated levels of steroids, CNIs, and mTORs, practitioners must adjust the dosing of these medications and carefully track their serum levels.

- A rise in liver enzymes, particularly in decompensated cirrhosis, and pancreatitis have also been reported with its use in HIV patients. Ritonavir is an inhibitor of CYP3A4 and to a lesser extent CYP2D6, as well as an inhibitor of intestinal glycoprotein P. The majority of immunosuppressants are metabolized by CYP450 isoenzymes and eliminated via glycoprotein P. For instance, tacrolimus and cyclosporine are metabolized by this system, while mycophenolic acid is metabolized by uridine diphosphate glucuronosyltransferase (UGT) and has fewer

- Several studies have reported a significant increase in the plasma concentration of tacrolimus (8–20-fold) when used with PIs. Therefore, based on the available evidence on HIV-positive kidney and liver recipients, who received tacrolimus and lopinavir concurrently, the recommended dose of tacrolimus is 0.5 mg every 5–7 days and its plasma concentration should be maintained between 6 and 8 ng/mL. If daily administration of tacrolimus is preferred, the dose of 0.03–0.08 mg daily or a reduction to one-twentieth to one-fiftieth of baseline daily dose is recommended.

- Another CNI, cyclosporine, has less severe drug interactions with PIs than tacrolimus, but an increase in its plasma concentration, particularly when used with hydroxychloroquine, is of great importance. Thus, based on studies conducted on HIV-positive kidney and liver recipients who received cyclosporine and lopinavir/ritonavir concurrently, the cyclosporine dose should be reduced to one-fifth of the total daily dose to achieve 100–200 ng/mL as the target plasma concentration (eg, 25 mg every 1–2 days), and daily plasma concentration measurement is also recommended.

- As mentioned earlier (see “Immunosuppressive Medications”, above), temporary discontinuation of mTOR inhibitors in transplant patients with COVID-19 at the discretion of the transplant team is recommended. However, if they are continued, the drug interaction with PIs should be noted, and a 50–90% reduction in dose of sirolimus and discontinuation of everolimus should be considered in concurrent use with PIs.

RIBAVIRIN

- If this drug is administered in transplant patients with COVID-19, the risk of drug interactions and adverse effects should be noted. Hemolytic anemia 1–2 weeks after the initiation of ribavirin, particularly in combination with interferons, is of great importance. Patients with cardiovascular comorbidity need more attention regarding this adverse effect.

- The concurrent use of ribavirin with bone marrow suppressant drugs, such as antimetabolites, cotrimoxazole, ganciclovir, and valganciclovir, which may be used in transplant patients, causes thrombocytopenia and pancytopenia.Considering renal elimination of ribavirin, its use is not recommended in patients with a GFR <50 mL/min because the risk of hemolytic anemia increases.

REMDESIVIR AND UMIFENOVIR (ARBIDOL)

- Remdesivir, which is an adenosine analogue and RNA polymerase inhibitor, acts as an antiviral agent and has been successful in the treatment of MERS-CoV and ebola in clinical and animal models. Thus, this drug has been mentioned in some studies as one of the treatment options for COVID-19 and its efficacy in COVID-19 is under investigation in clinical trials.

- There are no known drug interactions between remdesivir any of the commonly used immunosuppressive agents taken by SOT recipients. However, transplant practitioners should be cautious when administering remdesivir to SOT patients with COVID-19 given the lack of studies evaluating its safety in this patient population. Particular caution must be taken in liver transplant recipients and other SOT recipients who may be at heightened risk of hepatic injury from remdesivir as well as those with chronic kidney disease, usually a major comorbidity in this population. Nevertheless, there is general agreement that the potential benefits outweigh the potential risks of using remdesivir in SOT recipients with COVID-19, provided they meet the general guidance contained in the EUA.

- The AASLD has warned about its hepatotoxic effects in transplanted patients.
- Umifenovir is another potential option for COVID-19 treatment. It is a broad-spectrum antiviral agent used in the treatment and prevention of influenza and it has in vitro activity against SARS-CoV-2. Studies published after the emergence of SARS-CoV-2 indicate that it has positive effects on COVID-19, in combination with other therapeutic options.

- The suggested dose in one study is 200 mg every 12 hours for 10 days.In a case report regarding two kidney transplant patients with COVID-19 who were treated successfully, umifenovir was one of the therapeutic options.
- Umifenovir is metabolized by the liver, particularly CYP3A4, so it should be used with caution in patients with liver failure.Its protein binding is high; thus, it should be used cautiously in patients receiving other medications with high protein binding.So far, no data are available regarding its effects when used concurrently with immunosuppressants.

- IFN type I, such as IFN-α and IFN-β, and IFN type II, such as INF-γ, are considered important components of the host immune response to viral infections. Interferons have been used in the treatment of hepatitis C virus (HCV) in combination with ribavirin, owing to their positive effect on viral replication and immunomodulatory properties. After the emergence of SARS-CoV-1 in 2003 and MERS-CoV in 2013, studies regarding the effects of IFNs in their treatment have been conducted. Currently, IFNs are being studied for the treatment of COVID-19.

- IFNs have been used as nebulization or subcutaneous injections in these studies. Although it is too early to make judgments about the efficacy of IFNs in the management of COVID-19, the following points should be considered in kidney or liver transplant recipients with COVID-19 for whom INFs are initiated.

- Long-term use of IFNs may cause bone marrow suppression, so it is recommended not to use these agents in severe neutropenia or thrombocytopenia. Moreover, their use can lead to hepatotoxicity. There are several reports of hepatoencephalopathy, jaundice, and acute liver failure in patients receiving IFN for the treatment of HCV.

- At the same time, acute and chronic rejection, plasma cell hepatitis, and consequently graft failure have been reported in liver transplant recipients using pegylated interferon. Also, acute humoral rejection in kidney transplant recipients with HCV treated with IFN has been reported. Therefore, IFNs are not recommended in kidney and liver transplant recipients because of the risk of rejection.

INTERLEUKIN (IL) ANTAGONISTS

- A hyperinflammatory syndrome, which presents with fulminant and fatal hypercytokinemia, is mentioned as COVID-19 pathogenesis in the majority of studies conducted in this regard. Some studies have mentioned positive effects of IL-1 inhibitor (anakinra) and IL-6 antagonist (tocilizumab) in COVID-19, and clinical trials are being conducted to evaluate the efficacy of these agents in the management of this disease.

- Thus, we should wait for the results of these studies. Studies on the safety of tocilizumab in transplantation have so far been restricted to steroid-refractory acute graft-versus-host disease (GVHD), and studies regarding the safety of this agent in kidney and liver transplantation are limited.

- Although studies on the efficacy and safety of tocilizumab in transplantation are scarce, some case reports have indicated that the use of monotherapy or combination therapy with tocilizumab improved the status of transplant recipients with COVID-19. It is worth mentioning that some aspects of tocilizumab administration, such as time of initiation (early vs late phase), route of administration (subcutaneous vs intravenous), and dose, are not clear yet, and we have to wait for the results of clinical trials.

- We found case reports mentioning liver damage and fulminant liver failure due to hepatitis B reactivation following tocilizumab therapy. However, there are some studies reporting successful treatment by tocilizumab of chronic antibody-mediated rejection in kidney transplant patients.Considering the specific adverse effects of tocilizumab, including upper respiratory tract infections, cardiovascular complications, and hepatic failure, it seems that until an official announcement of the results of ongoing studies, its use in transplant patients with COVID-19 is

CONVALESCENT PLASMA

- P has historically been considered a safe treatment with relatively few adverse side effects, including among SOT recipients. In the epidemics influenza A H1N1, SARS-CoV-1, and MERS-CoV, studies did not find any adverse effects consistently associated with CP. Similar to any other human blood product, CP can cause various allergic and transfusion-related reactions such as anaphylaxis, hemolysis, transfusion-associated circulatory overload, and transfusion-related acute lung injury. In trials investigating CP for COVID-19, adverse events have included fevers, chills, anaphylaxis, and transfusion-related acute lung injury .. CP does not interact with any immunosuppressive medications prescribed to SOT patients and evidence for the use of CP to treat COVID-19 in SOT patients is limited to case reports

OTHER CONSIDERATIONS

- Sometimes, medications other than antivirals are used for symptomatic therapy or supportive care in COVID-19 patients. For the management of fever, myalgia, or headache caused by COVID-19 or by medication such as hydroxychloroquine, acetaminophen (paracetamol) is recommended as the first line agent, but acetaminophen-induced hepatotoxicity should be noted and the dose should be no more than 2 g/day.

- Regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patients, no conclusive evidence is available. The mechanism of action of NSAIDs includes inhibition of cyclooxygenase (COX)1/COX2. These enzymes are responsible for the production of prostaglandins (PGs), such as PGE_2/PGD_2 and PGI_2, which can promote and restrain inflammation. It is reported in one study that inflammation worsens following NSAID administration in COVID-19 patients, particularly those receiving ibuprofen.

- In one study, ibuprofen induced overexpression of ACE2 in diabetic rats.This effect can theoretically worsen the inflammatory course in patients suffering from COVID-19. However, some studies have concluded that owing to the anti-influenza properties of naproxen, it may be effective in COVID-19 patients.

- Also, considering the antiviral activity of indomethacin on coronavirus replication in vitro, it may be effective in COVID-19 patients.It is too early to make judgments about the effects of NSAIDs in the management of COVID-19 patients, and particularly transplant recipients, and we should wait for the results of ongoing studies, but the following points should be considered in the management of COVID-19 in kidney and liver transplant recipients.

- Administration of NSAIDs in kidney transplant patients increases the risk of acute kidney injury (AKI) owing to their mechanism of action (inhibition of PG synthesis) and decrease in renal blood flow.The risk of AKI increases with the concurrent use of CNIs as the basis of immunosuppression in kidney transplant recipients. Also, concern exists regarding NSAID administration in liver transplant patients, particularly due to diclofenac liver injury.Thus, caution should be applied when administering NSAIDs in transplant recipients.

- Another complication in patients with COVID-19 is nausea and vomiting (N/V). Serotonin antagonists (5-HT_3 receptor antagonists), dopamine antagonists, NK1 antagonists, and antihistamines are common drugs used for the management of N/V.

- Considering polypharmacy in patients with COVID-19, special attention should be given to drug interactions between antiemetics and other administered medications when treating N/V in this population. For instance, the risk of QT prolongation is high in concurrent use of lopinavir/ritonavir, hydroxychloroquine, and serotonin antagonists, such as ondansetron and granisetron, or NK antagonists, such as aprepitant, and it is better to avoid their concurrent use.

- Furthermore, serotonin syndrome is predictable in concurrent use of serotonin antagonists with some common medications in critically ill patients, such as linezolid and fentanyl. Therefore, considering the safety of antiemetics, it is recommended to use antihistamines, such as diphenhydramine or dimenhydrinate, in patients with COVID-19. Also, it is advised to administer medications such as lopinavir/ritonavir after meals, and to insert an interval of at least 1 hour between these agents and emetogenic drugs, such as oseltamivir.

- Dry cough is the main complaint of patients with COVID-19. Dextromethorphan, guaifenesin, codeine, and levocloperastine are safe in majority of patients and do not have any potential drug–drug interactions. However, the risk of serotonin syndrome with high-dose administration or prolonged use of dextromethorphan or other agents that increase serotonin should be noted.

- In transplant patients with cardiovascular diseases and COVID-19, it is necessary to continue cardiovascular medications. Based on animal laboratory studies, ACE2 receptors in the lung are binding sites for SARS-CoV-2. At first, the hypothesis was considered that taking ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) can worsen the pulmonary function of patients with COVID-19, but further studies demonstrated that ACEIs or ARBs can be considered as potential therapeutic options for the management of patients with COVID-19.

- Therefore, cardiovascular disease societies recommend that patients taking ACEIs or ARBs continue receiving their treatment and avoid the abrupt discontinuation of these drugs due to adverse effects on the course of COVID-19 disease.

- Statins are another prescribed class of medications discussed in patients with COVID-19. Considering their anti-inflammatory properties, positive clinical experience with statins in the improvement of ARDS in patients with ebola and MERS, and their effect in upregulation of the activity of the ACE2 pathway, some reports have recommended their use in patients with COVID-19.

- We should wait for further studies regarding the prescription of statins in kidney and liver transplant patients with COVID-19. Also, the side effects of statins, such as a rise in liver enzymes, myalgia, or, in more severe cases, rhabdomyolysis, should be considered. Considering drug interactions between immunosuppressants and statins, it seems that tacrolimus is a safer option than cyclosporine in concurrent use of atorvastatin.

- It is worth mentioning that most statins are metabolized via CYT P450 isoenzymes, particularly 3A4, as well as P-glycoproteins. The coadministration of PIs, such as lopinavir and darunavir, and their pharmacokinetic enhancers, such as ritonavir and cobicistat, with statins leads to increased statin levels and their adverse effects. Simvastatin or lovastatin should not be administered concomitantly with ritonavir/cobicistat-boosted PIs. The maximum recommended daily dose of atorvastatin and simvastatin is 20 and 10 mg, respectively, when coadministered with ritonavir/cobicistat-boosted PIs

OTHER INVESTIGATIONAL AGENTS

- One novel agent under investigation for treatment and post-exposure prophylaxis of COVID-19 is REGN-CoV2. REGN-CoV2 is a cocktail of two virus-neutralizing antibodies that non-competitively bind the critical receptor binding domain of the S protein of SARS-CoV-2, neutralizing the virus and preventing infection [80]. In a recent statement from Regeneron, there are three ongoing late-stage trials on REGN-CoV2 being performed in collaboration with the National Institute of Allergy and Infectious Diseases: two phase 2/3 trials for the treatment of hospitalized and ambulatory patients with COVID-19 that will evaluate virologic and clinical endpoints and one phase 3 trial for post-exposure prophylaxis in individuals who have had a high-risk exposure to someone with confirmed COVID-19.

- Other agents include favipiravir, famotidine, nitazoxanide, ribavirin, ivermectin, zinc, and others]. Famotidine, which may act to inhibit the 3CL protease, has been found to be associated with reduced rick of clinical deterioration leading to intubation or death among hospitalized patients with COVID-19. Favipiravir is a broad-spectrum antiviral that inhibits viral RNA polymerase that is also being investigated as a potential therapeutic for COVID-19 . These medications remain primarily investigational with limited data to support their use beyond clinical trials.