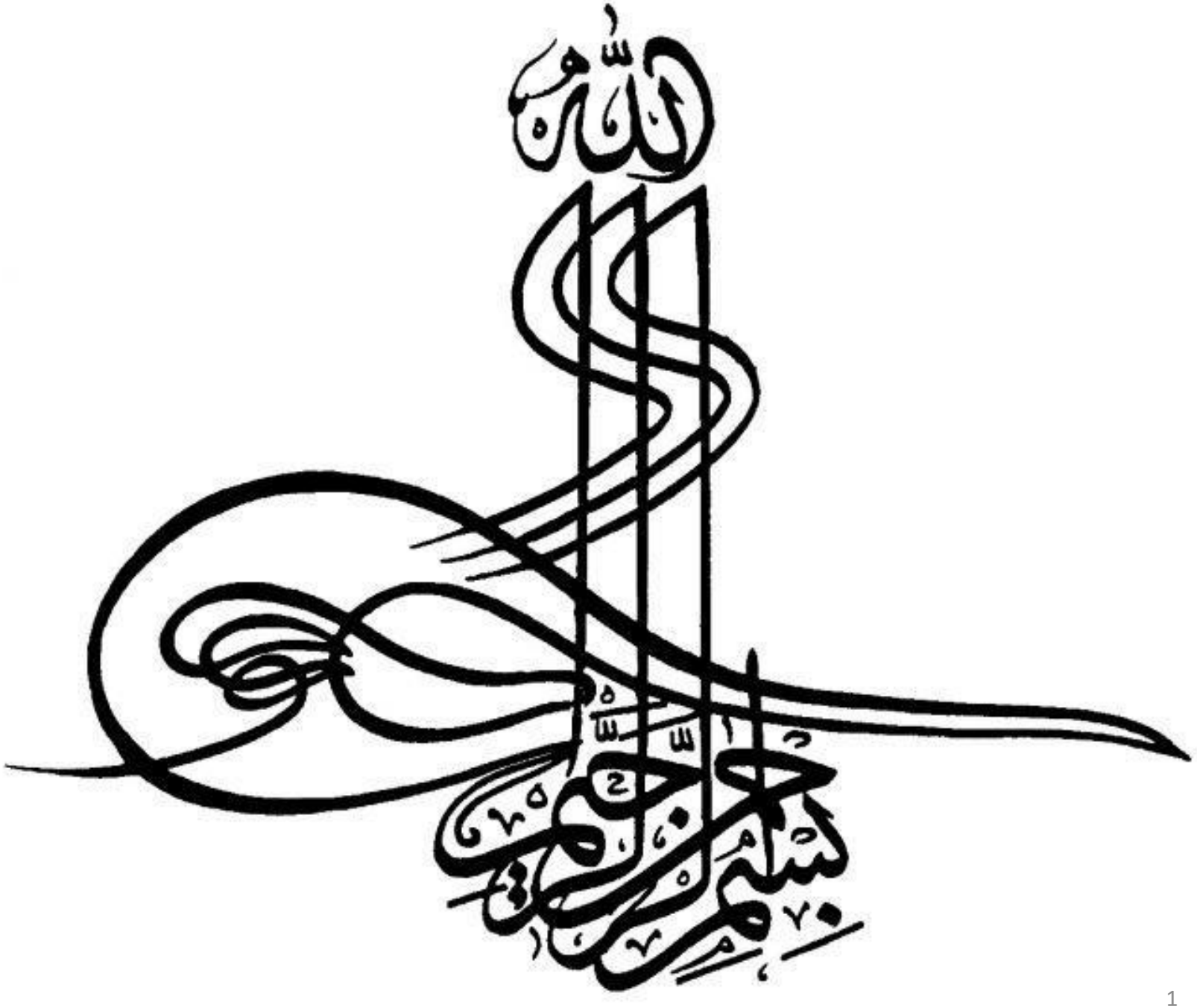
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بسم الله الرحمن الرحيم

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CNIs and Antimetabolite Drug Interactions

- Pharmacokinetic drug interactions (Substance A affects the absorption, distribution, metabolism, or excretion of substance B)

- Pharmacodynamic drug interactions (Substance A enhances or antagonizes the intended effect of substance B)
  - Additive Toxicity

    (Substance A enhances the adverse effects of substance B)

Pharmacokinetic Drug-Drug Interactions

Absorption:

- Only drugs which alter the extent, but not the rate of immunosuppressive absorption are clinically important.

- Food has no effect on MPA AUC, but it delays the absorption and decreases MPA Cmax by 40% and 33% when mycophenolate mofetil and mycophenolate sodium, respectively, are administered.
- Consistency in administration of the calcineurin inhibitors with regard to meals and food intake is important to sustain an effective concentration time profile. High-fat meals can enhance both plasma clearance and the volume of distribution of cyclosporine by more than 60%.43 Food reduces the rate and extent of tacrolimus absorption, and a high-fat meal may further delay gastric emptying and reduce the maximum achieved serum concentration (Cmax), and the AUC
  - Food significantly reduces the rate and extent of Tacrolimus absorption.
    - Tacrolimus should be taken on an empty stomach to increase oral absorption.
  - Gastrointestinal absorption of cyclosporine and tacrolimus can be affected by adding a prokinetic agent.

Pharmacokinetic Drug-Drug Interactions

- **Absorption**
  - Product A binds with product B in the GI tract (CNIs, Sir, MMF)
    - Cholestyramine, colestipol, probucol, sevelamer
  - Most common example is chelation of agents with di/trivalent metals
    - E.g. **Ca, Al, Zn, Mg, multivitamins, antacids chelate MMF, ERL, FK-506, prednsione**
  - Result = decreased effectiveness of both
  - Management= separate doses (2 hour before or 4 hours after)

Orlistat significantly ↓the absorption of Cyc

Pharmacokinetic Drug-Drug Interactions

- Distribution
  - Least common type of pharmacokinetic interaction

PHARMACOKINETICS

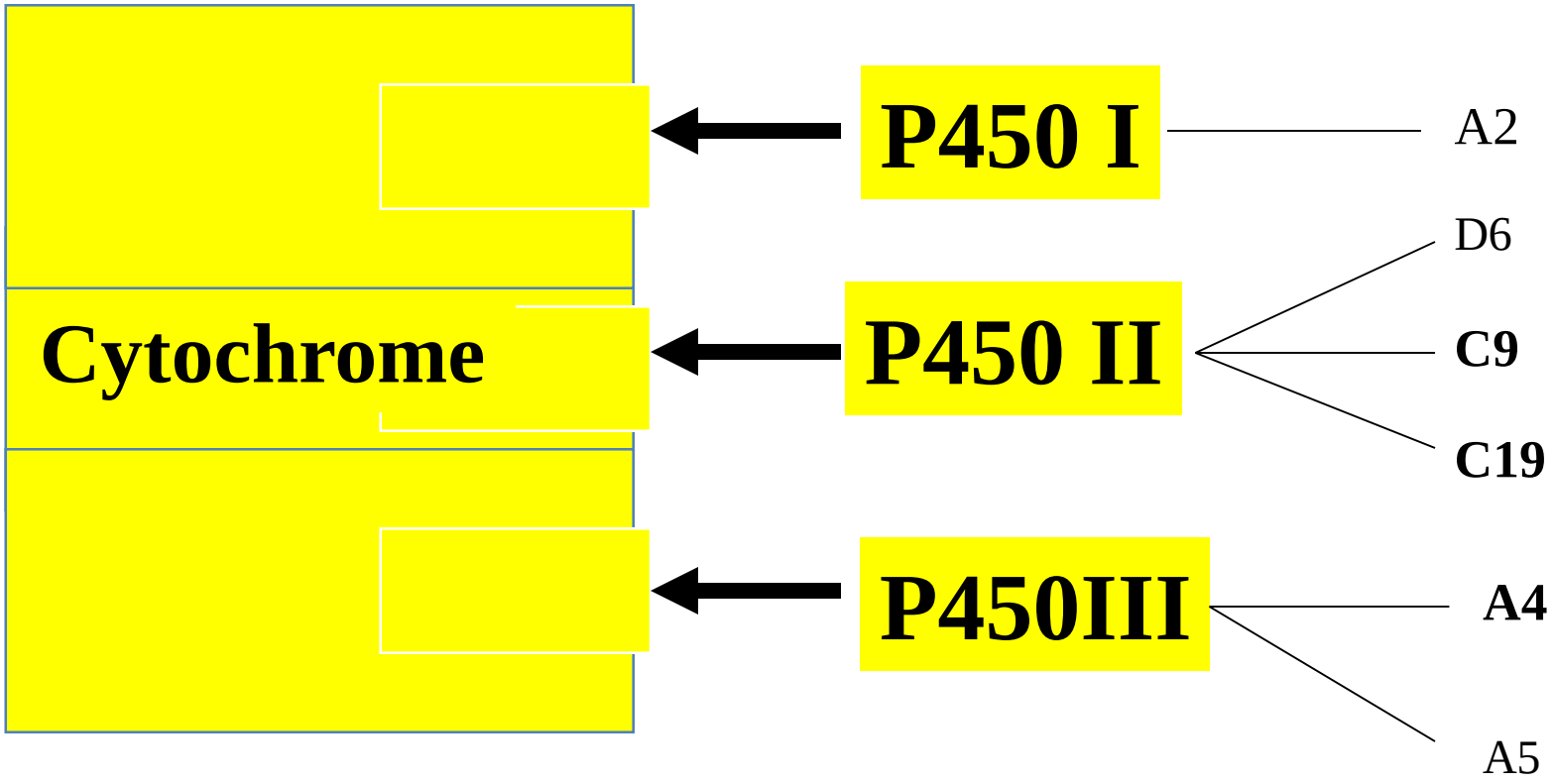
Metabolism

– The most common type of PK drug interaction

1. Cytochrome P-450 isoenzymes
    1. Inhibitors
    2. Inducers

2. P-glycoprotein transporter

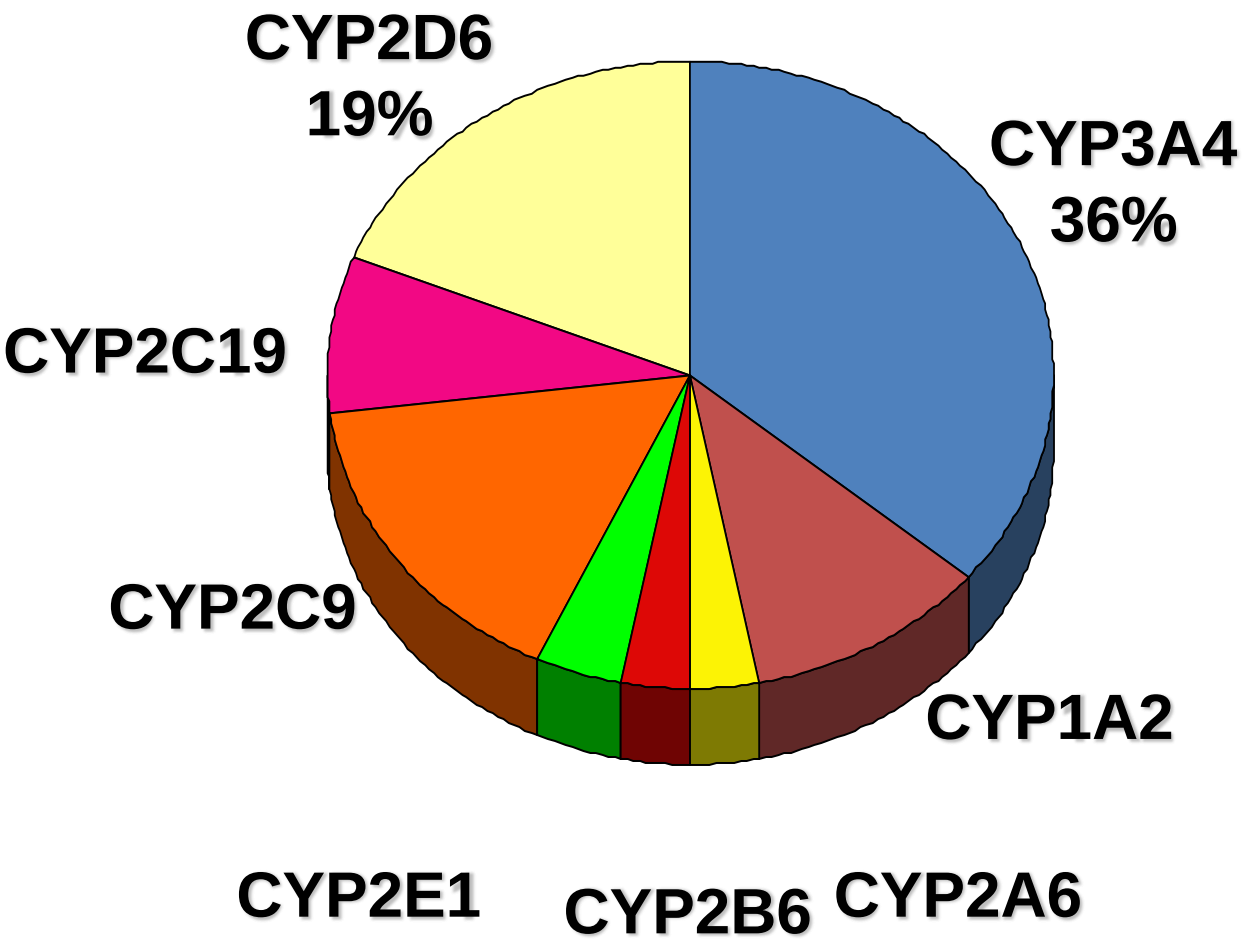
Cytochrome P450



Pharmacokinetic Drug Interactions

- Hepatic enzymes – **Cytochrome P 450 system** metabolizes numerous drugs
  - Many different isoenzymes
    - 3A4, 2C9, 2C19, 2D6, and 1A2 most common
    - 3A4 most clinically significant
- Many drugs **induce** or **inhibit** certain hepatic enzymes
- Many drugs are **substrates** of the CYP 450 system

Proportion of Drugs Metabolized by CYP450 Isozymes



Pharmacokinetic Drug Interactions

Metabolism

- Drugs that **induce CYP450**
  - **Decrease** the concentrations of other drugs metabolized by CYP 450 (results in decreased therapeutic effects)

- Drugs that **inhibit CYP450**
  - **Increases** in the concentrations of other drugs metabolized by CYP450 (may increase risk of adverse effects)

P-Glycoprotein Transporter

- Transmembrane efflux pump
- Tumor cell overexpression → chemotherapy resistance
- Intestinal site → reduced drug absorption
- BBB prevents CSF distribution
- Proximal tubular epithelium → increased urinary excretion

P-Glycoprotein AND CYP 3A4

- Co-localize to liver and intestine
- Decrease intracellular drug concentrations
- Drug “interaction”
  - Decreased metabolism / decreased efflux
  - High degree of shared substrate

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

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(*Ther Drug Monit* 2020;00:1–9)

- 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 immunosup pressive drugs.

- 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

- 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)

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 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—not recommended	Major—not recommended	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]

(HYDROXY)CHLOROQUINE

- PD and PK interaction

PROTEASE INHIBITORS

- ✓ 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.
- ✓ With LPV/r co-administration, it has been suggested to decrease the SRL maintenance dose to 0.2mg/wk
- ✓ No data are currently available to support an important PK interaction between boosted PI regimens and MPA

Glucocorticoids

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

Recommendation: for patients who regularly use low-dose glucocorticoids for chronic diseases, a conservative but cautious attitude should be adopted with preservation or slight reduction of the usual dose.

Remdesivir

- ✓ 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 co-administration with remdesivir because of the lack of knowledge and studies evaluating the safety of co-administration.
- ✓ A strict TDM of ISD is therefore proposed especially since these drugs may be used in severe and rapidly evolving situations.

TOCILIZUMAB

- ✓ 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.

Favipiravir

- No information available

Interferone α/β

Research Article

JOURNAL OF HEPATOLOGY

Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C

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Review

OPEN

COVID-19 in Kidney Transplantation: Epidemiology, Management Considerations, and the Impact on Kidney Transplant Practice

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In KTRs, other specific antiviral medications have been used with variable success rates in several case series and reports from China and Europe. Several papers reported the use of the protease inhibitor combination of Lopinavir and Ritonavir.[33,56,57] In addition to an unlikely efficacy, their interaction with CNI metabolism suggests that this combination should not be used for the treatment of COVID-19 in KTRs.[58] Additionally, there is no proven benefit (and potential harm) of other agents such as intravenous immunoglobulin, interferon, HCQ, and azithromycin in KTRs except in anecdotal cases and their routine use is not recommended.[59]

Very early data from the general population suggest some efficacy for convalescent sera transfusions for patients with serious COVID-19 infections, although no such data are available yet for KTRs or other immunosuppressed patients.[27-31]