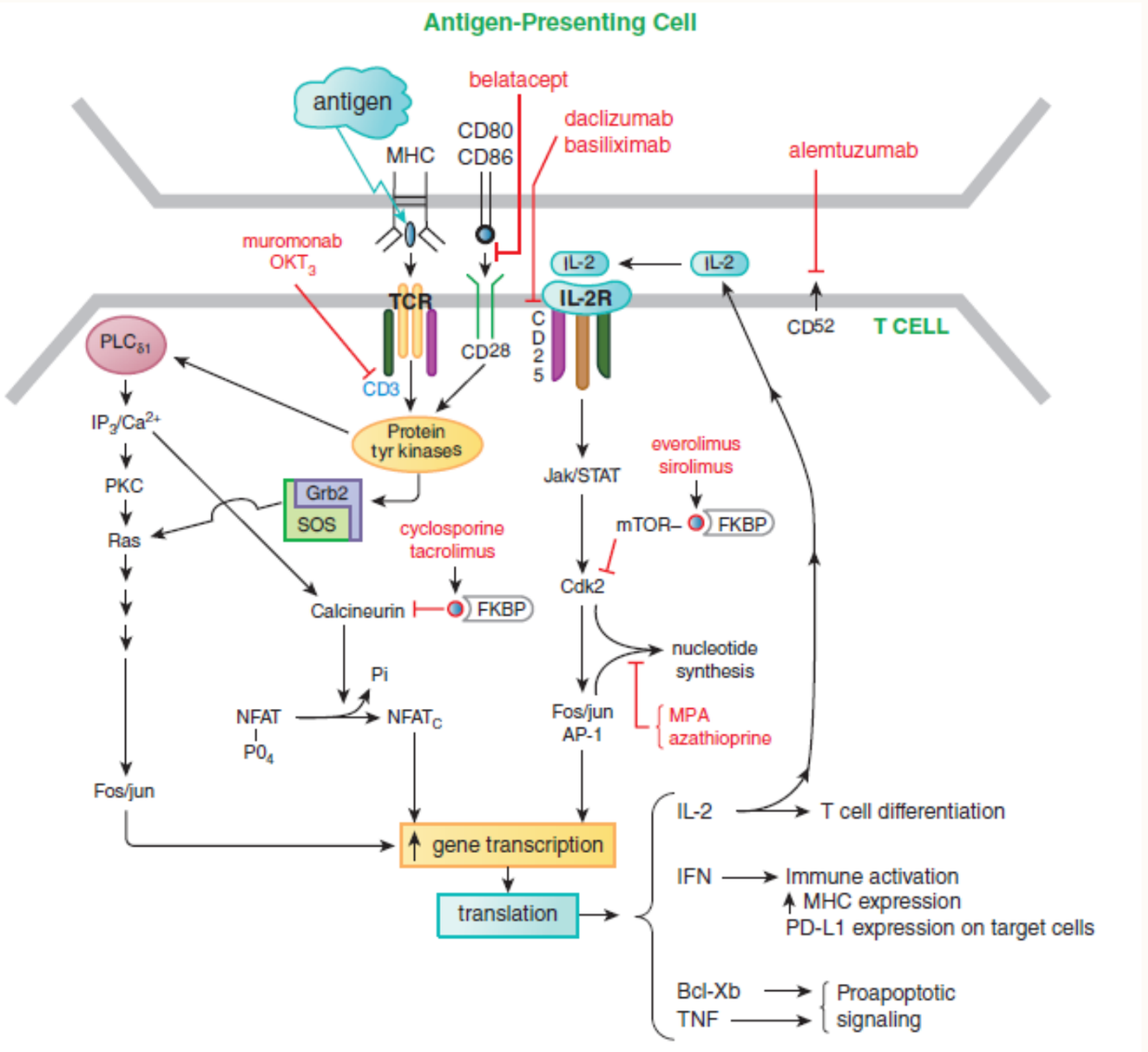
Optimizing Immunosuppres in Transplant Patients

A comprehensive overview for clinicians and pharmacists

Dr. Khosravi
Pharm-D, BCPS
HKC



Agenda

01

Introduction to Immunosuppression

Understanding the complexities of drug pharmacokinetics.

02

Maintenance Agents

CNI, mTORI, Antimetabolite

03

Formulations and Administration

Exploring different preparations and routes.

04

Pharmacokinetics and Therapeutic Drug Monitoring

Deep dive into drug behavior and monitoring strategies.

Maintenance Agents

❑ CNI

- ✓ Tacrolimus (TAC) - the most commonly used (approximately 90% of centers)
- ✓ Cyclosporine (CSA)

❑ ANTIMETABOLITE

- ✓ MMF
- ✓ MFA
- ✓ Azathioprine

❑ mTORI

- ✓ Sirolimus
- ✓ Everolimus

Tacrolimus: A Potent Immunosuppressant

- Formulations:
  - Immediate-Release (IR) Capsules: 0.5 mg, 1 mg, 5 mg (e.g., Prograf, Cograft, Suprotac)
  - Extended-Release (XR) Capsules: 0.5 mg, 1 mg, 3 mg, 5 mg (e.g., Advagraf, Envarsus XR)
  - Injection Solution Concentrate: 5 mg/mL (1 mL vial) for intravenous use.

Key Takeaway: While efficacy and safety are comparable between IR and ER formulations, important pharmacokinetic differences necessitate careful consideration during conversion or initiation.

Sublingual Administration: Short courses of sublingual tacrolimus have been utilized as an effective alternative to IV tacrolimus when enteral administration is not feasible, offering a bridge to oral therapy (**one-half** that required by the oral route).

Tacrolimus Formulations: Visual Guide

The **extended-release** products should be **taken at the same time of the day, preferably in the morning**.

Oral Administration Considerations

Empty Stomach Preference

Oral tacrolimus should ideally be administered on an empty stomach to optimize absorption and minimize variability.
0.08-0.1 mg/kg/day (**IBW**) orally in two divided doses

Consistency is Key

If not taken on an empty stomach, it is crucial to administer the dose consistently in relation to meals (e.g., always 1 hour after breakfast) to maintain stable drug levels.

Food-Drug Interactions

Food, particularly high-fat meals, can significantly reduce the bioavailability of tacrolimus due to its lipophilicity and dependence on gut absorption.

Tacrolimus Dose Conversion Guidelines

IV to Oral ER

First oral ER dose 8-12 hours after IV discontinuation. Trough levels should be monitored closely.

Oral IR to Oral ER (Advagraf)

Initiate ER at a 1:1 ratio (mg:mg) of the total daily IR dose. Readjust dose based on subsequent trough concentrations (C0) to maintain target levels.

Oral IR to IV

Administer 1/5th to 1/3rd of the total daily oral dose IV. Transition back to oral as soon as possible.
0.03-0.05 mg/kg/day continuous infusion

Steady State: Both tacrolimus and cyclosporine reach steady-state concentrations after approximately 4-6 doses. Therefore, dose adjustments can be reliably assessed via drug concentration monitoring 2-3 days after an adjustment, allowing for adequate time for new equilibrium.

Cyclosporine: Clinical Pharmacokinetics and Considerations

This presentation provides an in-depth look into the pharmacokinetics, administration, and clinical considerations of cyclosporine, a critical immunosuppressant in transplant medicine.

FORMULATIONS AND BIOAVAILABILITY

Nonmodified Cyclosporine (Sandimmun)

- Requires bile for absorption, leading to erratic GI absorption patterns.

Modified Cyclosporine (Neoral, Iminoral)

- Microemulsion formulation, independent of bile salts for absorption.
- Exhibits increased and more consistent bioavailability.

- Injection solution (50 mg/ml) (**non-modified**)
- Capsule 25, 50, 100 mg,
- Oral solution 100 mg/1 ml (50ml).

Clinical Precaution: Patients stabilized on one cyclosporine preparation should generally not be switched to another due to potential pharmacokinetic differences. If conversion is necessary, monitor trough concentrations until stable.

INTRAVENOUS CONVERSION GUIDELINES

Intravenous Cyclosporine (CSA)

- **Conversion Ratio:** Approximately one-third of the total daily oral dosage, as IV administration bypasses first-pass metabolism.

- **IV Dose Range:** 0.5 to 2 mg/kg/day (**IBW**)
- **Administration:** Can be given as a continuous infusion or as a single or twice-daily injection.

Accurate conversion between oral and intravenous routes is essential for maintaining therapeutic drug levels and preventing both rejection and toxicity in transplant recipients when oral administration is not feasible.

DISTRIBUTION AND PROTEIN BINDING

Cyclosporine (CSA)

- **Protein Binding:** Primarily binds to lipoproteins in plasma, but also to erythrocytes and lymphocytes.
- **Distribution:** Widely distributed into tissues and body fluids.
- **Volume of Distribution (Vd):** High, ranging from 3-5 L/kg, reflecting extensive tissue uptake.

Tacrolimus (TAC)

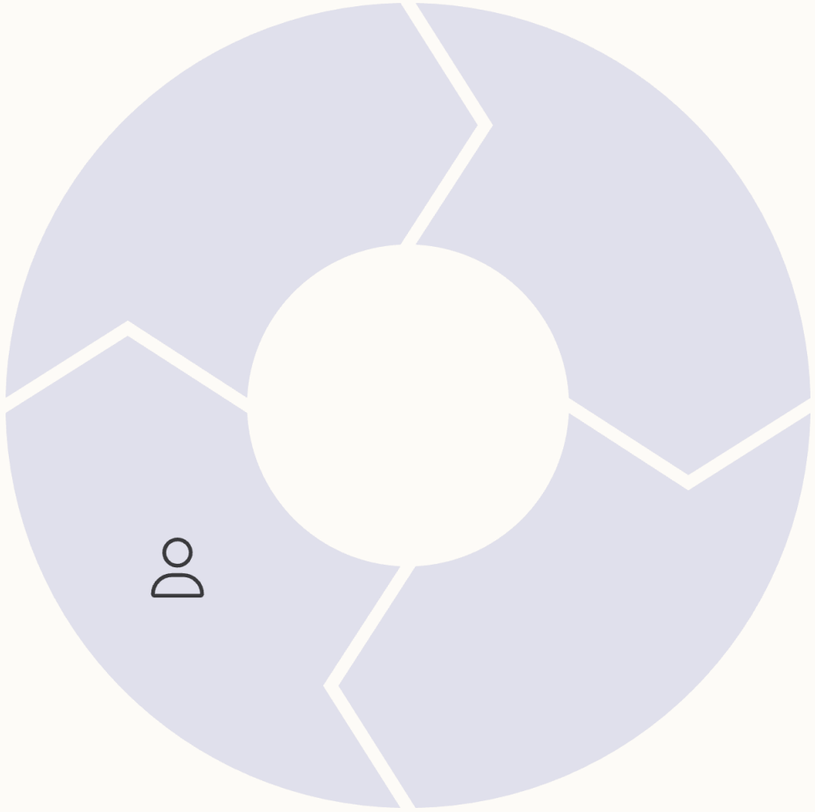
- **Protein Binding:** Binds mainly to albumin and alpha-1-acid glycoprotein, and significantly to red blood cells (RBCs) due to high affinity for FKBP12.
- **Distribution:** Primarily distributed within the vasculature.
- **Volume of Distribution (Vd):** Lower than CSA, typically 0.8-1.9 L/kg, due to significant RBC binding.

Unlike tacrolimus, CSA depends on bile for intestinal absorption, which further increases inter- and intra-patient variability.

METABOLISM AND ELIMINATION

Hepatic Metabolism

Cyclosporine is extensively metabolized by CYP3A4 enzymes in both the gut and liver.



P-Glycoprotein (P-GP), OATP Transport

Actively transported by P-glycoprotein, impacting absorption and elimination.

Enzyme Inhibitor

Cyclosporine acts as an inhibitor of both CYP3A4 and P-GP.

Half-Life

The average elimination half-life is approximately 15-20 hours.

Genetic polymorphisms in CYP3A5 significantly impact metabolism of TAC.

Therapeutic Drug Monitoring (TDM) of Tacrolimus

Purpose of Monitoring

TDM prevents toxicity, optimizes efficacy, and assesses patient adherence to the prescribed regimen, establishing a critical concentration-efficacy-toxicity relationship.

Primary Parameter: Trough Concentration (C0)

Trough concentrations correlate well with overall total body exposure (Area Under the Curve, AUC), making them the primary clinical monitoring parameter.

Target Trough Ranges

0-3 month: 8-12 ng/mL
3-6 month: 7-10 ng/mL
> 6 month: 5-7 ng/mL

Analytical Method

Most centers now use mass spectrometry (e.g., **HPLC** with mass spectrometry). This is a more reliable method as it specifically quantifies the parent drug, avoiding cross-reactivity with inactive metabolites.

Tacrolimus C0 Trough Target Levels in De Novo mTORi Regimens Post-Transplant

0-10 week	6-8 ng/ml
10-18 week	4-7 ng/ml
> 18 week	3-5 ng/ml

These target ranges for tacrolimus when used in conjunction with a de novo mTOR inhibitor regimen reflect a balance between effective immunosuppression and the reduction of potential toxicities. Close monitoring and individual patient response are crucial for optimal adjustment.

IMMUNOSUPPRESSANT MONITORING

Cyclosporine Trough Monitoring: A Cornerstone of Care

Cyclosporine concentrations are meticulously monitored to balance immunosuppression, prevent toxicity, and ensure patient adherence. While individual institutional protocols and patient-specific factors dictate precise ranges, maintaining target trough concentrations is paramount.

1

0-3 Months

C0: 150 to 300 ng/mL.
C2: 800-1200 ng/mL

2

3-6 Months

C0: 150 to 250 ng/mL.
C2: 800-1000 ng/mL

3

Beyond 6 Months

C0: 50 to 150 ng/mL.
C2: 400-800 ng/mL

Cyclosporine C0 Trough Target Levels in De Novo mTORi Regimens Post-Transplant

0-4 week	150-200 ng/ml
5-12 week	100-150 ng/ml
13-20 week	75-100 ng/ml
21-52 week	50-75 ng/ml
52+ week	25-50 ng/ml

Adjusting cyclosporine troughs in combination with mTOR inhibitors allows for reduced CNI exposure, mitigating long-term nephrotoxicity while maintaining effective immunosuppression. These guidelines are a starting point, requiring clinical judgment for individual patient needs.

Drug Interactions With Immunosuppressives

Some immunosuppressants, such as tacrolimus, exhibit highly variable pharmacokinetic profiles and narrow therapeutic indices. This variability underscores the critical importance of effective drug–drug interaction management in transplant recipients.

Drug interactions can be broadly categorized into two main types:

1

Pharmacokinetic

Occur when one medication alters the **absorption**, **distribution**, **metabolism**, or **elimination** of the immunosuppressant agent.

2

Pharmacodynamic

Involve interactions where drugs affect the body in **additive** or **synergistic** ways, influencing the efficacy or toxicity of immunosuppressants.

Immunosuppressant Drug Interactions

Immunosuppressant	Interacting Drugs	Mechanism	Consequence	Clinical Management
Calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus and everolimus	Clarithromycin,[a] erythromycin,[a] telithromycin,[a] ketoconazole,[a] itraconazole,[a] fluconazole, voriconazole,[a] fluoxetine, fluvoxamine, citalopram, nefazodone,[a] diltiazem,[a] verapamil,[a] delavirdine,[a] ritonavir,[a] cimetidine,[a] grapefruit juice,[a] amiodarone, saquinavir, nelfinavir, indinavir, amprenavir, chloramphenicol[a]	Inhibit CYP 3A isoenzyme in the liver and intestines.	Increase the blood concentration of the IS.	Either prospectively decrease the IS dose or monitor trough concentrations and AUC more closely and adjust doses accordingly.
Calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus and everolimus	Carbamazepine,[a] dexamethasone, phenobarbital,[a] phenytoin,[a] Saint-John's-wort,[a] rifampin,[a] rifabutin,[a] efavirenz,[a] nevirapine,[a] nafcillin, clindamycin	Induce CYP 3A4 isoenzyme in the liver and intestines.	Decrease the blood concentration of the IS.	Either prospectively increase the IS dose or monitor trough concentrations and AUC more closely and adjust doses accordingly.

Calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil, and mycophenolate sodium	Cholestyramine, colestipol, probucol, sevelamer, antacids (magnesium and aluminum containing), iron-containing products	Bind to IS and prevent absorption.	Decrease the blood concentration of the IS.	Avoid concomitant administration with IS and monitor trough concentrations.
Azathioprine	Allopurinol	Inhibit metabolism by inhibiting xanthine oxidase.	Increase the blood concentration of azathioprine.	Avoid use together or prospectively reduce azathioprine dose to one-third or one-fourth normal dose and monitor for increased toxicity.

Pharmacodynamic Interactions

Pharmacodynamic interactions involve altered physiological responses when medications are co-administered. For transplant patients, these interactions can significantly impact organ function and patient safety.

1 CNI + ACE Inhibitors

Concomitant use of Calcineurin Inhibitors (CNI) and ACE inhibitors can lead to increased potassium (K) and creatinine (Cr) levels, necessitating close renal function monitoring.

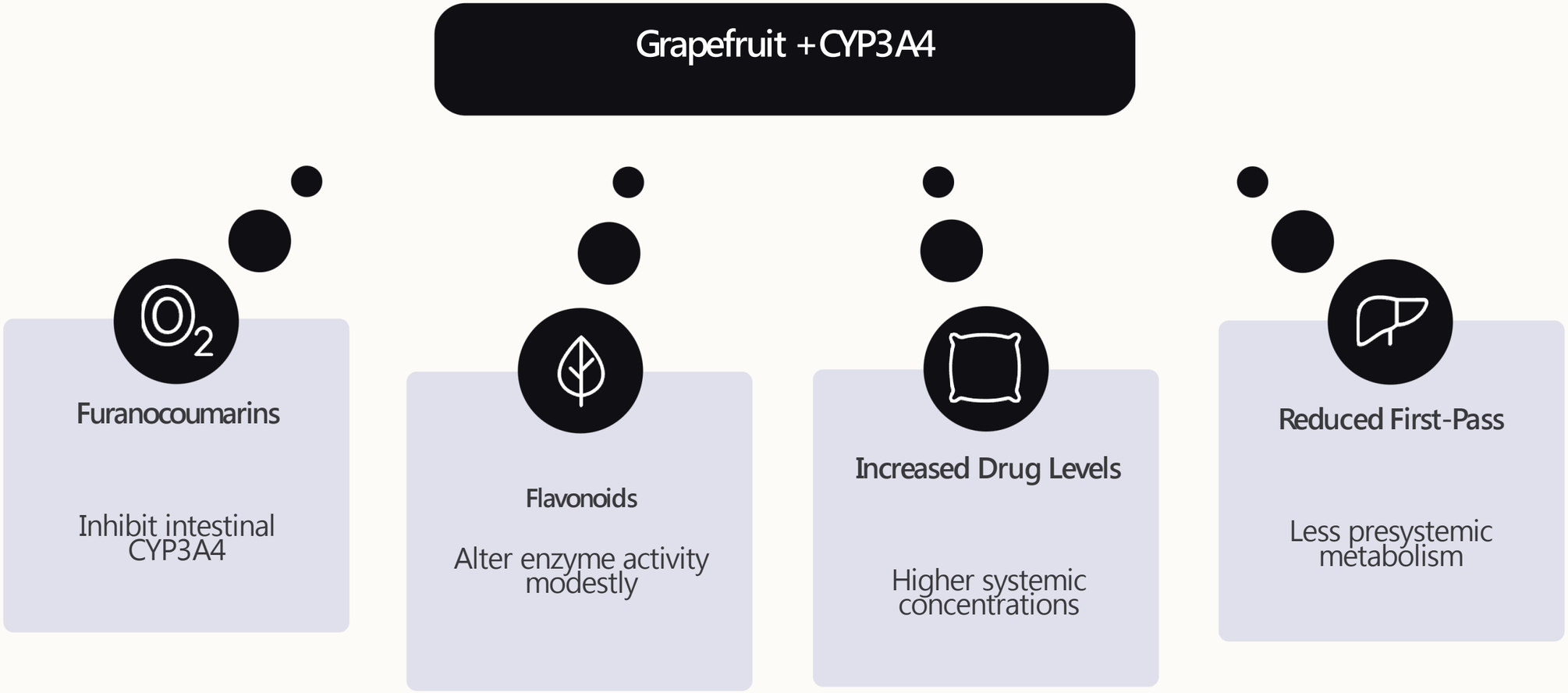
2 Metoclopramide and MMF

Metoclopramide combined with Mycophenolate Mofetil (MMF) can exacerbate gastrointestinal side effects, particularly diarrhea, due to altered gut motility.

3 Herbal Medications (Echinacea)

Herbal supplements like Echinacea can compromise the efficacy of immunosuppressant agents by stimulating the immune system, potentially leading to organ rejection.

GRAPEFRUIT JUICE INTERACTION



⚠ **Clinical Alert:** Patients on cyclosporine or tacrolimus should be advised to avoid grapefruit juice and related products due to the risk of clinically significant drug-drug interactions and subsequent toxicity.

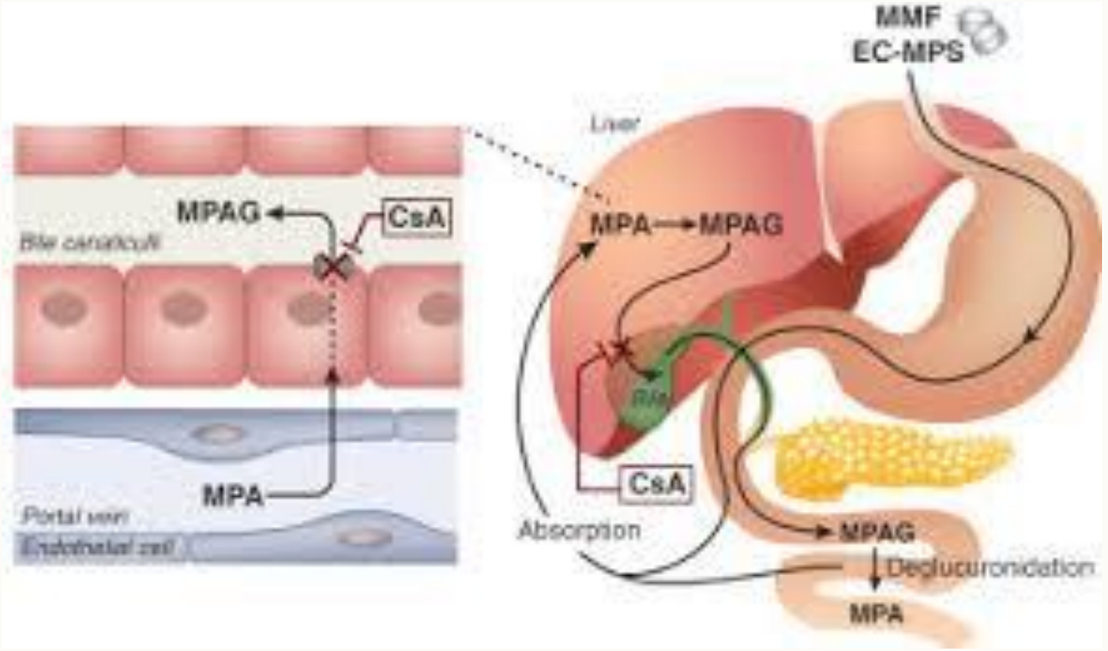
MYCOPHENOLIC ACID DERIVATIVES

Pharmacokinetics of Mycophenolate Mofetil (MMF)

MMF, a prodrug for mycophenolic acid (MPA), is a crucial component of many immunosuppressive regimens.

- **Absorption & Metabolism:** 94% bioavailability and rapidly **hydrolyzed** to **MPA**, with Cmax occurring at 1-3 hours. MPA is primarily **glucuronidated** to inactive **MPAG**, which is **renally** eliminated but also undergoes significant **enterohepatic recycling**.

- **Enterohepatic Recycling:** MPAG excreted into bile can be deconjugated back to MPA in the GI tract, leading to a **second MPA peak** at 6-12 hours. This recycling is **inhibited by cyclosporine**, significantly lowering MPA AUC when co-administered.



Half-life & Protein Binding: MPA has an average elimination half-life of 17 hours, a volume of distribution of 4 L/kg, and is 98% protein-bound to albumin.

Free MPA concentrations correlate with immunosuppressive effect.

CLINICAL CONSIDERATIONS

Mycophenolate Adverse Effects & Management

Mycophenolic acid derivatives are generally well-tolerated, but clinicians must be vigilant for common adverse effects, particularly gastrointestinal and hematologic complications.

1 Gastrointestinal Issues

- Anorexia, nausea, vomiting, and diarrhea are common.
- Strategies: administer without other meds, smaller frequent doses, or dose reduction with gradual titration.

2 Hematologic Complications

- Leukopenia, thrombocytopenia, and anemia can occur.
- If WBC count <3000 or ANC <1300 cells/mL, reduce or discontinue MMF.

3 Infections

Increased susceptibility to infections, especially at higher dosages, necessitates careful monitoring.

Adverse effects are more prevalent with higher dosages. Patient education and proactive management are key to optimizing adherence and outcomes.

Dosing and Administration of Mycophenolic Acid

1

Formulations

Mycophenolate mofetil is available in **oral and IV forms**, while mycophenolate sodium is oral-only. that IV and oral mofetil are not bioequivalent despite similar AUCs.

MMF

Cap 250, 500 mg/ Inj 500 mg

Powder for suspension oral 1 g/5 ml

MPA

Tab 180, 360 mg

2

Dosing Regimen

MPA is typically administered in two divided doses every 12 hours for optimal immunosuppression and reduced adverse effects.

3

Target Doses

- **Kidney/Liver: 2 g/day (mofetil), 1.44 g/day (sodium)**
- Heart: 3 g/day (mofetil), with a target trough >1.5 µg/mL
- **Pediatric: 600 mg/m² (mofetil), 400 mg/m² (sodium), divided doses**

MONITORING DEBATES

MPA Therapeutic Drug Monitoring: Current Perspectives

Routine therapeutic drug monitoring (TDM) for MPA plasma concentrations remains a topic of debate due to **inconsistent data on improved patient outcomes**. However, specific scenarios suggest potential benefits.

Correlation with Rejection

Low MPA AUCs and troughs in kidney transplant recipients have been linked to acute rejection episodes, suggesting some predictive value.

Target Ranges

For centers that routinely monitor MPA, typical AUC0-12 targets are **30-60 µg·h/mL**, with trough concentrations of **1-3.5 µg/mL**.

Utility in CNI-Sparing Protocols

MPA monitoring appears more beneficial in protocols involving calcineurin inhibitor (CNI) sparing, withdrawal, or minimization, where MPA plays a more prominent immunosuppressive role.

Mycophenolate Mofetil (MMF) Monitoring Challenges

Effective monitoring of Mycophenolate Mofetil (MMF) is crucial, though complexities exist in accurately assessing drug exposure.

1

AUC as Gold Standard

The Area Under the Curve (AUC) is considered the most reliable measure of mycophenolic acid (MPA) drug exposure.

2

Limitations of Trough Levels

Single-point sampling, particularly early post-dose trough levels (C0), shows poor correlation with the comprehensive AUC, indicating their limited utility for accurate exposure prediction.

3

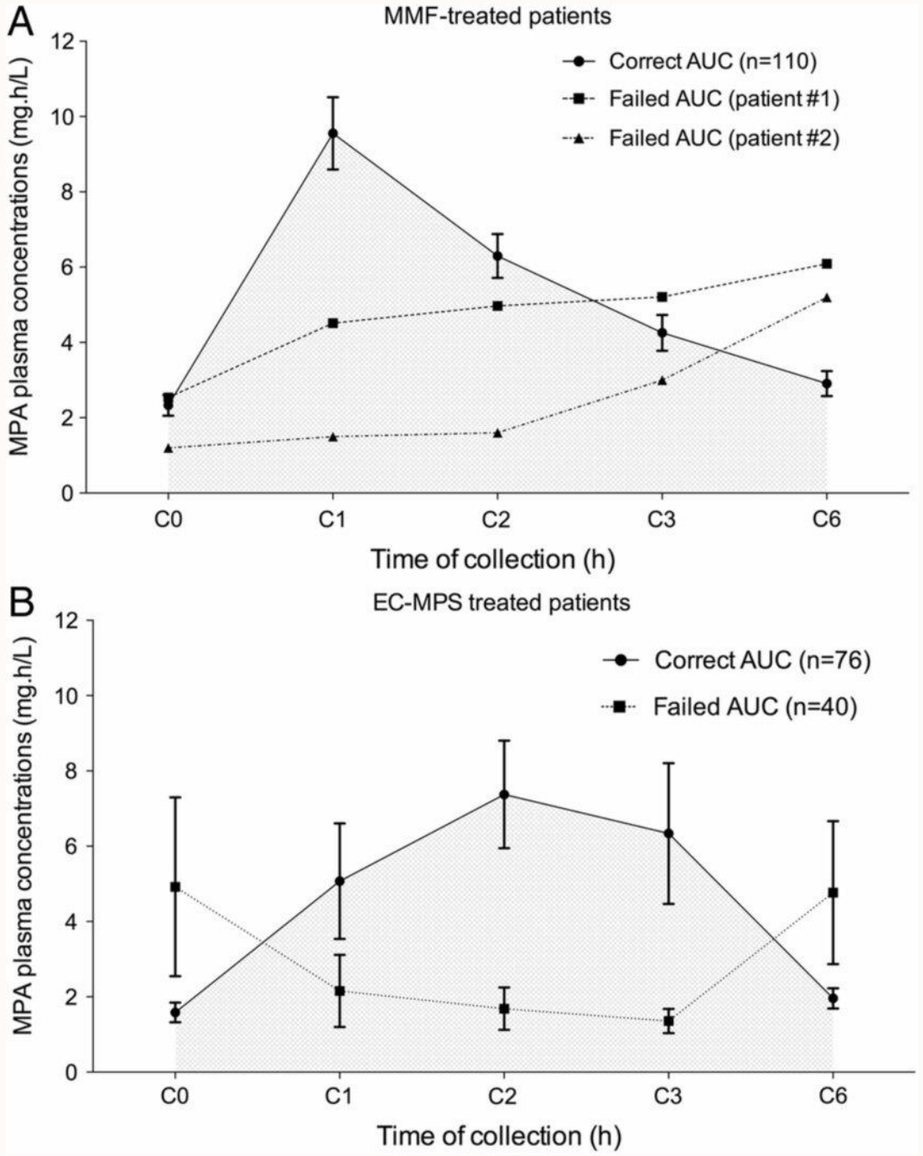
Limited Sampling Strategies

To overcome single-point limitations, studies investigate limited sampling strategies, typically using 2-4 sampling points (e.g., between 2 and 4 hours post-dose) to predict the AUC more effectively.

Why is this important?

Accurate drug exposure assessment is essential for preventing both under-immunosuppression (leading to rejection) and over-immunosuppression (leading to toxicity), especially given the narrow therapeutic index of MMF.

KDIGO 2009: MMF Therapeutic Window



MPA AUC0–12 Therapeutic Window

The proposed therapeutic window for Mycophenolic Acid (MPA) **AUC0–12** is **30–60 µg·h/mL.** This target range is specifically applicable during the early post-transplant period and when MMF is used in combination with Cyclosporine (CsA).

Correlation with MPA C0

In patients co-treated with CsA, an MPA **C0** (12-hour trough concentration) range of **1.0–3.5 mg/L** generally correlates with the desired MPA AUC0–12 of 30–60 µg·h/mL. This correlation provides a practical, albeit imperfect, surrogate for assessing overall drug exposure.

PHARMACOKINETIC INFLUENCERS

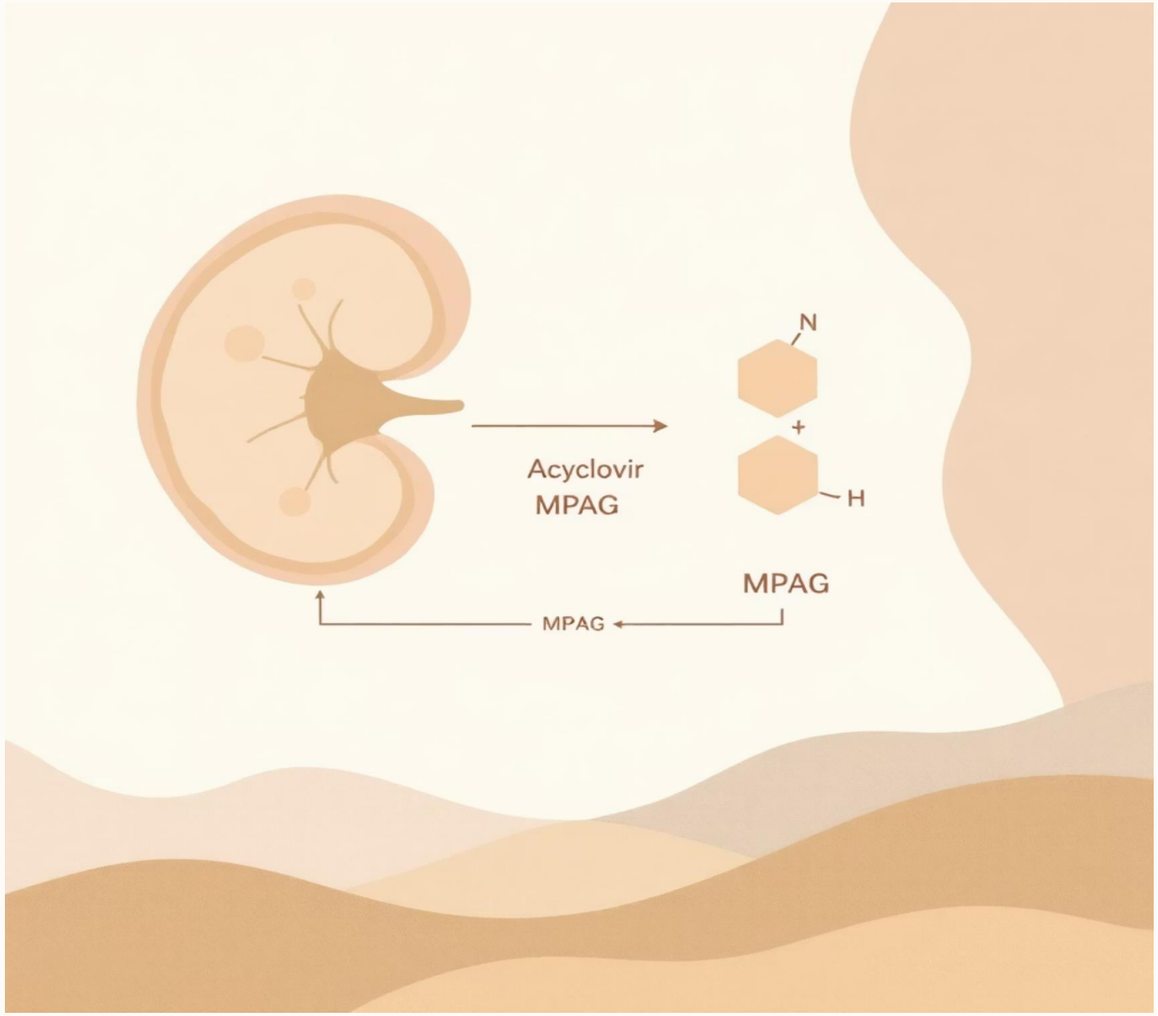
Mycophenolate: Drug-Drug & Drug-Food Interactions

Food (MMF)	Delayed absorption, 40% decrease in Cmax	Potentially impacts early exposure, but AUC remains unchanged.
Food (Mycophenolate Sodium)	Delayed absorption, 33% decrease in Cmax	Potentially impacts early exposure, but AUC remains unchanged.
Aluminum- & Magnesium-containing Antacids	Decreases MPA AUC	Likely not clinically significant.
Iron	Potential for similar results (not tested)	Theoretical, but exercise caution.
Pantoprazole (with MMF)	Decreases MPA concentrations & systemic exposure	Clinically significant in healthy volunteers; monitor patients closely.
Pantoprazole (with Mycophenolate Sodium)	No observed effect	No significant interaction.

Understanding these interactions is crucial for optimizing mycophenolate dosing and minimizing variability in drug exposure, ultimately contributing to better patient outcomes.

Acyclovir and Mycophenolic Acid: A Competitive Dance in the Kidney

Acyclovir/ Valacyclovir ➲ competes with Mycophenolic Acid Glucuronide (MPAG) for renal tubular secretion ➲ ↑ AUC for both drugs when co-administered ➲ ↑ bone marrow suppression.



Pharmacokinetic Profile of mTOR Inhibitors

Mammalian Target of Rapamycin (mTOR) inhibitors, sirolimus and everolimus, are critical immunosuppressants. Understanding their pharmacokinetic properties is crucial for optimizing therapeutic outcomes and minimizing adverse effects.

Oral Bioavailability

Low, typically 14-20%. Peak concentrations are achieved within 1-2 hours.

Volume of Distribution

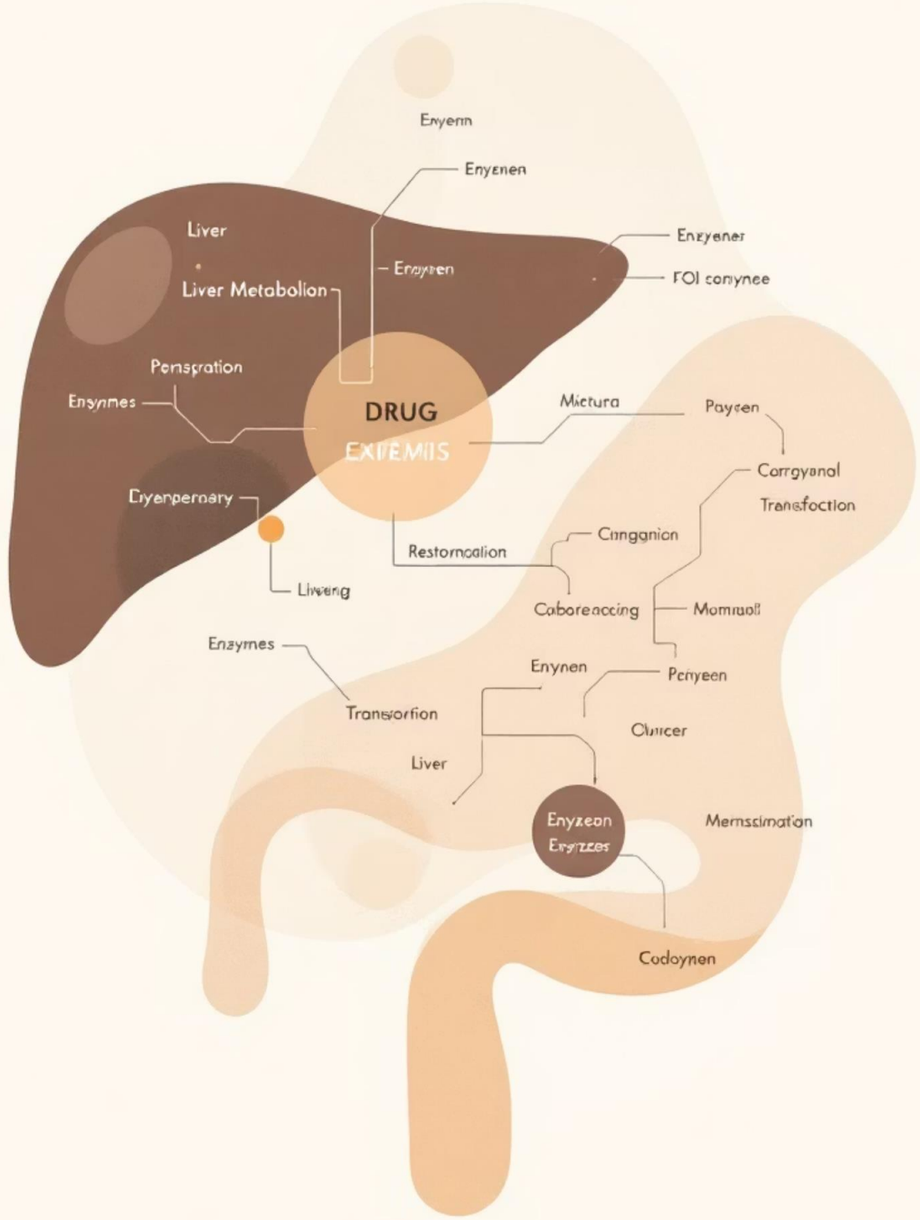
Both exhibit large volumes: 5.6-16.7 L/kg for sirolimus and 128-529 L for everolimus, indicating **extensive tissue distribution**.

Metabolism

Primarily metabolized by **CYP3A4** in the gut and liver. Both are also **substrates for P-glycoprotein**.

Half-Life

Sirolimus: 60 hours (up to 110 hours with liver dysfunction). Everolimus: 18-35 hours.



Drug-Drug and Drug-Food Interactions

> The primary metabolic pathway for both everolimus and sirolimus is CYP3A4, making them susceptible to significant drug interactions through CYP3A4 induction or inhibition.

Sirolimus & Cyclosporine (CSA)

- ✓ CSA + sirolimus ➲ ↑ sirolimus CSA AUC and trough concentrations ➲ **4 hours seperate**
- ✓ Proposed mechanism: Competitive binding to CYP3A4 and P-glycoprotein.

Everolimus & Cyclosporine (CSA)

- ✓ A single dose of microemulsion CSA increased everolimus AUC.
- ✓ **No specific recommendations for dose timing are provided.**

Dietary Considerations and mTOR Inhibitors

Grapefruit Juice Interaction

Similar to cyclosporine and tacrolimus, grapefruit juice significantly increases sirolimus concentrations. This effect is due to CYP3A4 inhibition and necessitates strict avoidance to prevent toxicity.

Impact of High-Fat Meals

- **Sirolimus**: Administration with a high-fat meal leads to a delayed absorption rate, decreased Cmax, and increased AUC, resulting in greater overall drug exposure ➲ administer consistently (± food), once daily dosing

- **Everolimus**: Conversely, a high-fat meal decreases both Cmax and AUC for everolimus, suggesting reduced drug exposure.

Dosing and Administration Strategies

Precise dosing and consistent administration are critical for achieving and maintaining therapeutic levels of mTOR inhibitors, balancing efficacy with safety.

01

Sirolimus Dosing

Previously approved fixed dosing regimens with cyclosporine included loading doses of 6-15 mg followed by **2 mg daily**. However, loading doses are no longer recommended due to increased side effects.

02

Sirolimus Monitoring (C0)

Therapeutic drug monitoring (TDM) is routinely performed using whole-blood concentrations measured by HPLC, ensuring specific detection of the parent compound and guiding dose adjustments.

Target serum concentrations for Sirolimus are **3-8 ng/mL.**

03

Everolimus Dosing

A starting dose of **0.75 mg twice daily** is indicated for regimens including **CSA**, and **1.5 mg twice daily** for regimens including **TAC**

04

Everolimus Monitoring Targets (C0)

Target serum concentrations for everolimus are **3-8 ng/mL** , which are essential for guiding therapeutic decisions and ensuring optimal immunosuppression.

Sirolimus Target Levels Post-Transplant (+MMF/MPA)

C0 (ng/ml)	Month
0-3	10-15
>3	5-10

Combined Tacrolimus and Sirolimus Target Levels Post-Transplant

	TAC	SIR
0-2 week	8 ng/ml	3-4 week
2-4 week	6-8 week	3-4 week
5-8 week	6 week	4-5 week
9+ week	4-6 week	4-5 week

The synergistic effect of sirolimus and tacrolimus allows for lower target concentrations of each drug, potentially reducing individual drug toxicities while maintaining robust immunosuppression. These combined targets offer a framework for balancing efficacy and safety throughout the post-transplant period. SIR

Sirolimus: Administration and Side Effects

Drug interactions are similar to CSA

Common Side Effects

- **Impaired wound healing:** A significant concern, particularly in the post-operative period.
- **Metabolic disturbances:** Hypercholesterolemia and hypertriglyceridemia are common and often require lipid-lowering agents or dose reduction.
- **Hematologic effects:** Leukopenia and thrombocytopenia are **dose-related**.
- **Renal effects:** Associated with **proteinuria** in kidney transplant recipients; monitoring is recommended, and use is generally avoided in patients with pre-existing proteinuria.
- **Other notable effects:** Lymphedema, oral ulcerations, diarrhea, arthralgias, epistaxis, rash, acne, nausea, vomiting, lymphocele, hypokalemia, anemia, hypertension, **pneumonitis**, reproductive endocrine disorders, and increased infection risk.

Thank You

Does anyone have any questions?