

Maintenance of Immunosuppression Part One

Kimberly Harrison, Pharm.D., BCPS, BCTXP
Cardiothoracic Transplant Clinical Specialist
Vanderbilt University Medical Center
Nashville, Tennessee



1

Disclosures

- I have nothing to disclose.



2

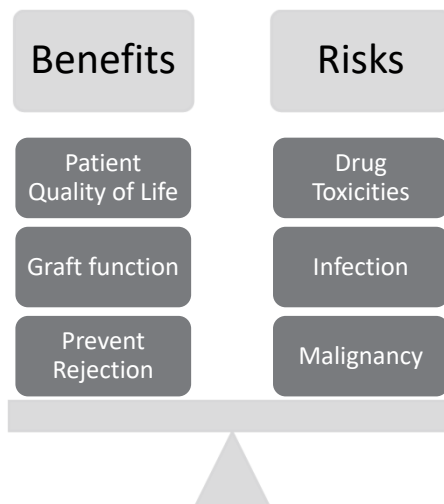
Learning Objectives

1. Differentiate between the pharmacokinetic profiles of immunosuppressive medication formulations utilized in solid organ transplantation.
2. Select the appropriate method for therapeutic drug monitoring of immunosuppressive medications.
3. Design an initial immunosuppression regimen for a solid organ transplant recipient utilizing a patient's pharmacogenomic data.
4. Revise an immunosuppression regimen for a solid organ transplant recipient based on the presence of pertinent drug-drug interactions.
5. Assess patient-specific data to identify immunosuppression-related adverse effects.
6. Design an appropriate monitoring plan for immunosuppressive medications.

3

Maintenance Immunosuppression

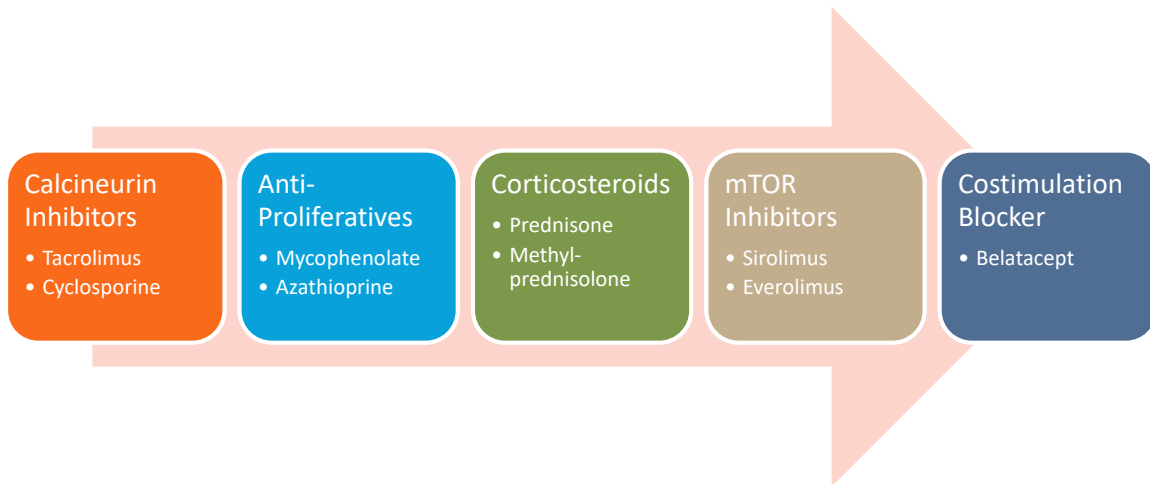
- Chronic therapy
- Initiated at the time of transplant
- Requires vigilant monitoring



Am J Health Syst Pharm. 2012;69(22):1961-75.

4

Presentation Overview

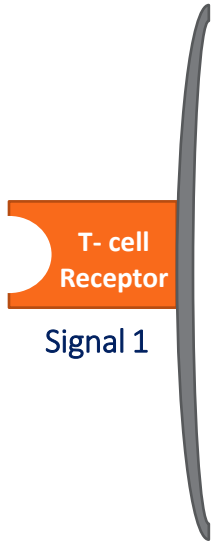


5

Calcineurin Inhibitors (CNIs)

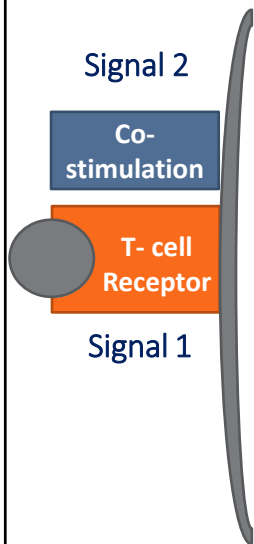
6

Calcineurin Inhibitor Mechanism of Action

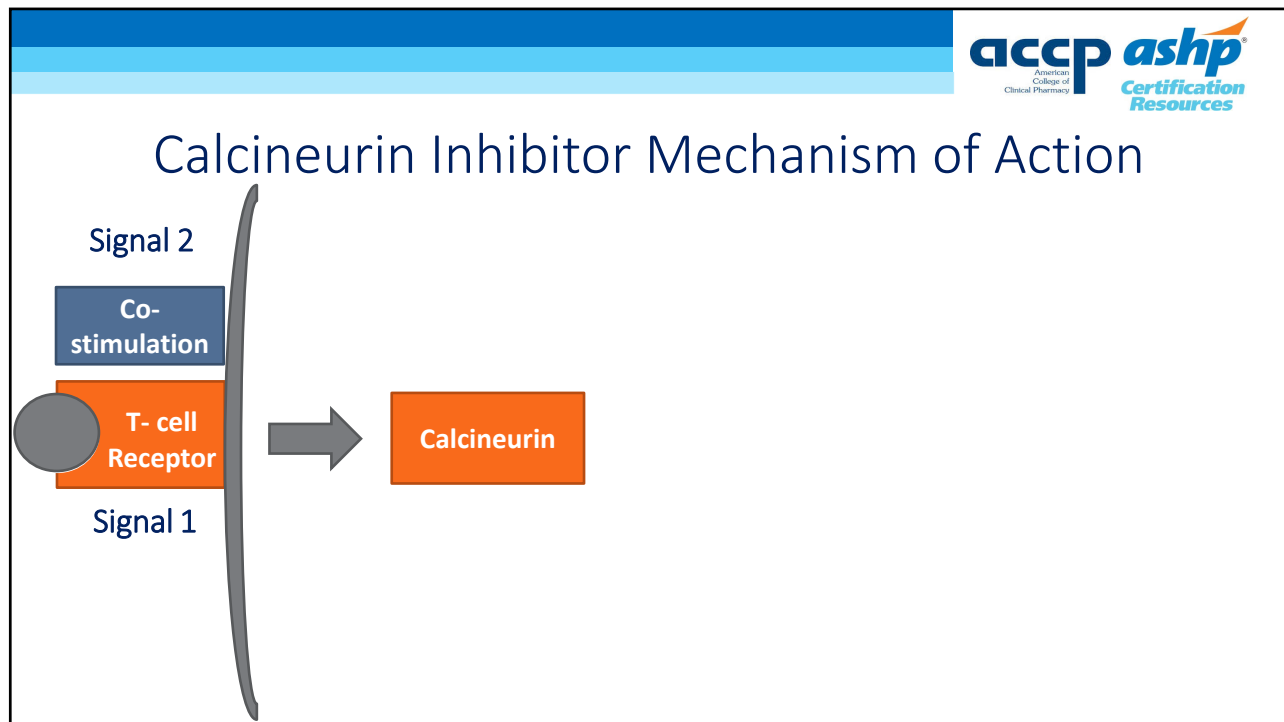


7

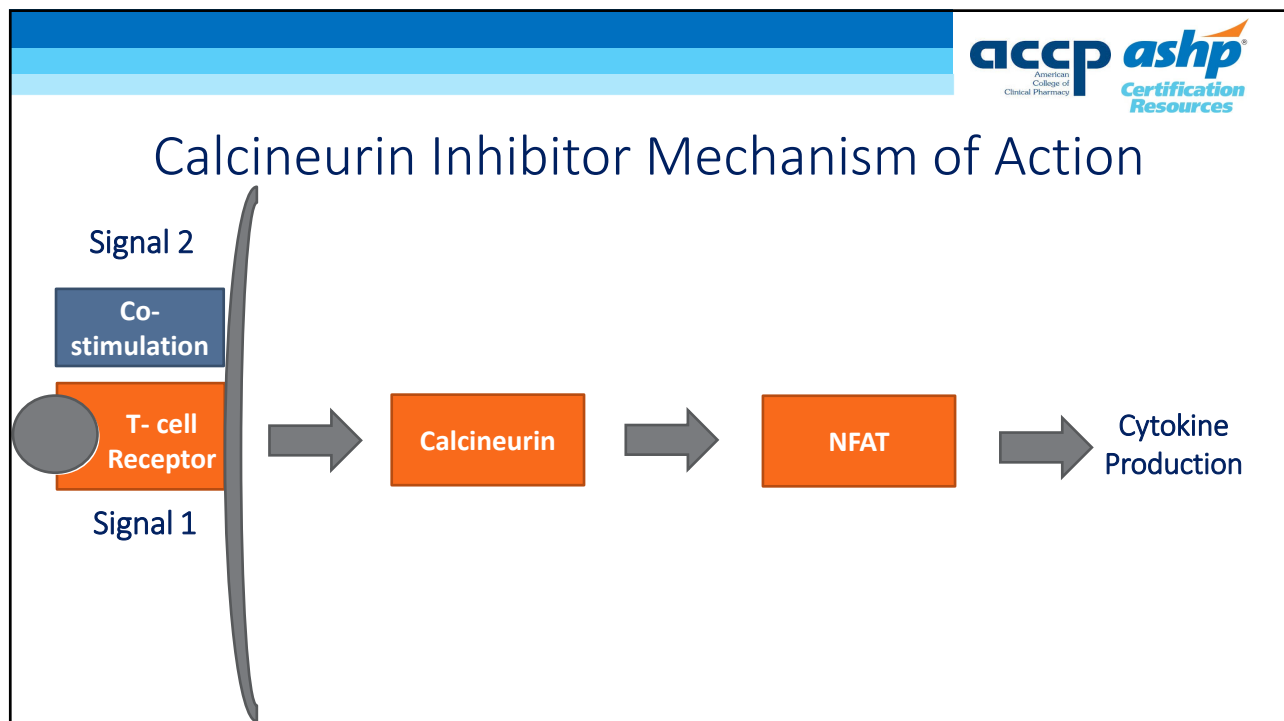
Calcineurin Inhibitor Mechanism of Action



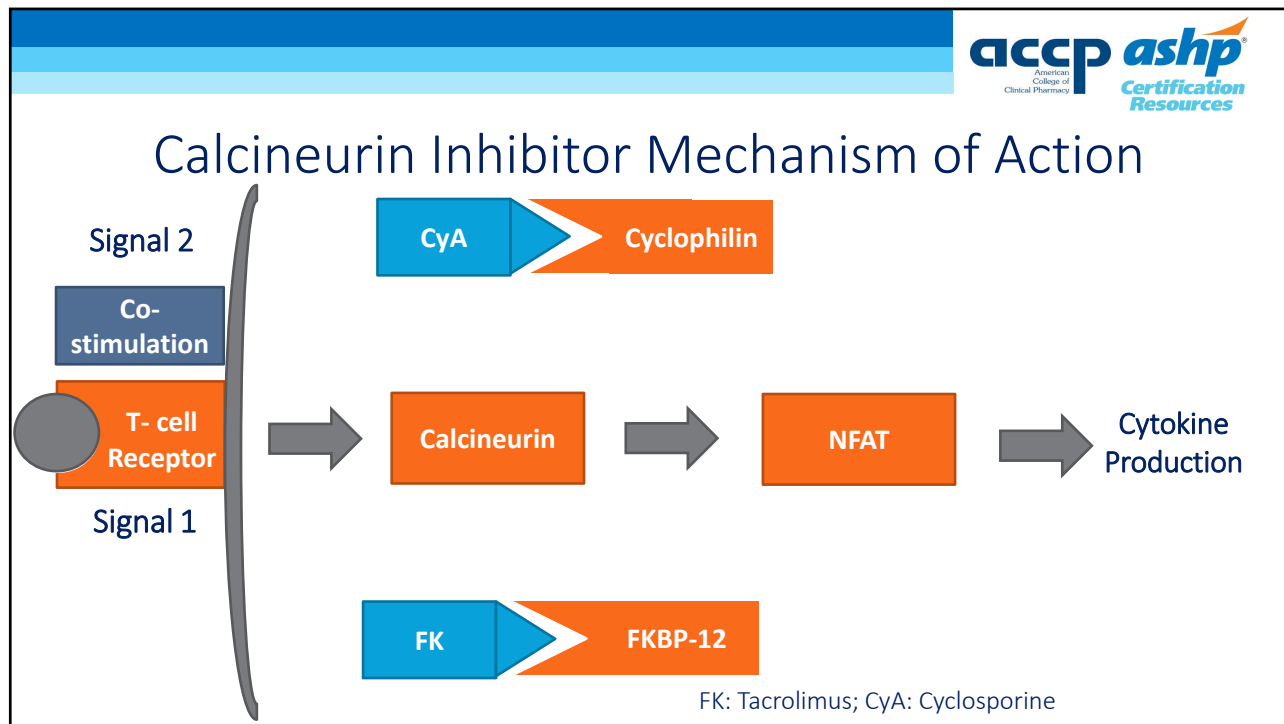
8



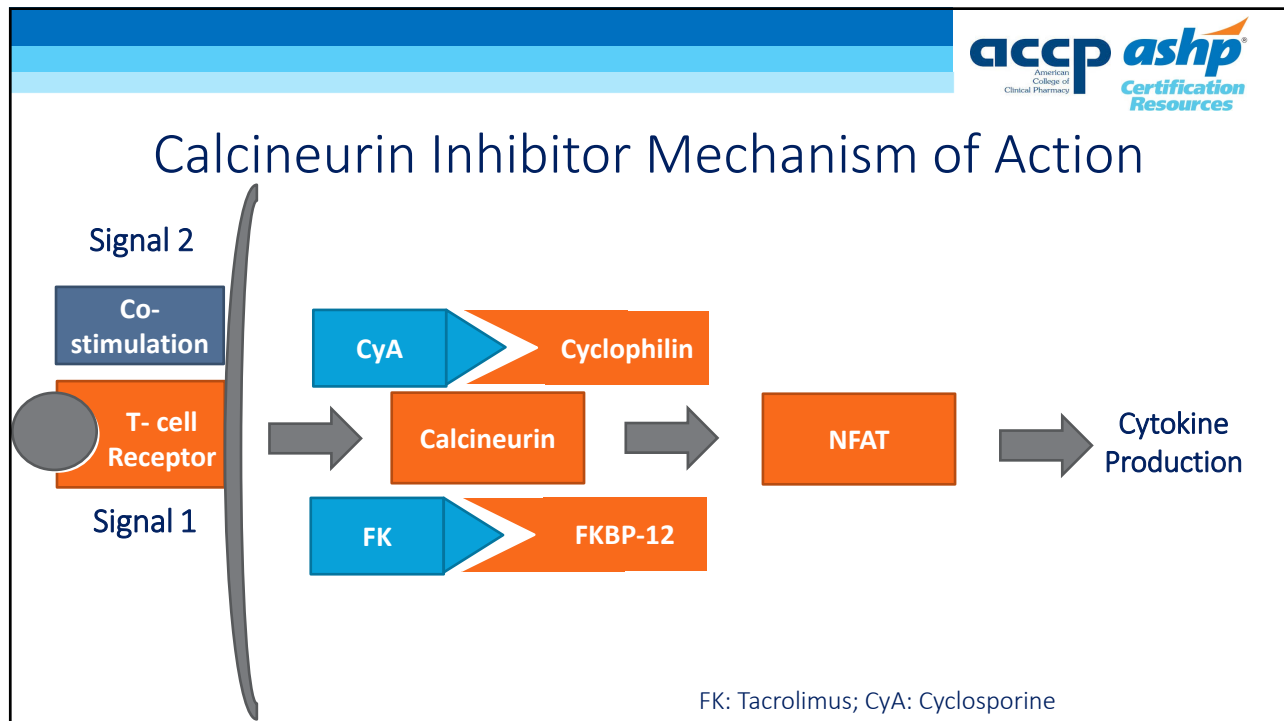
9



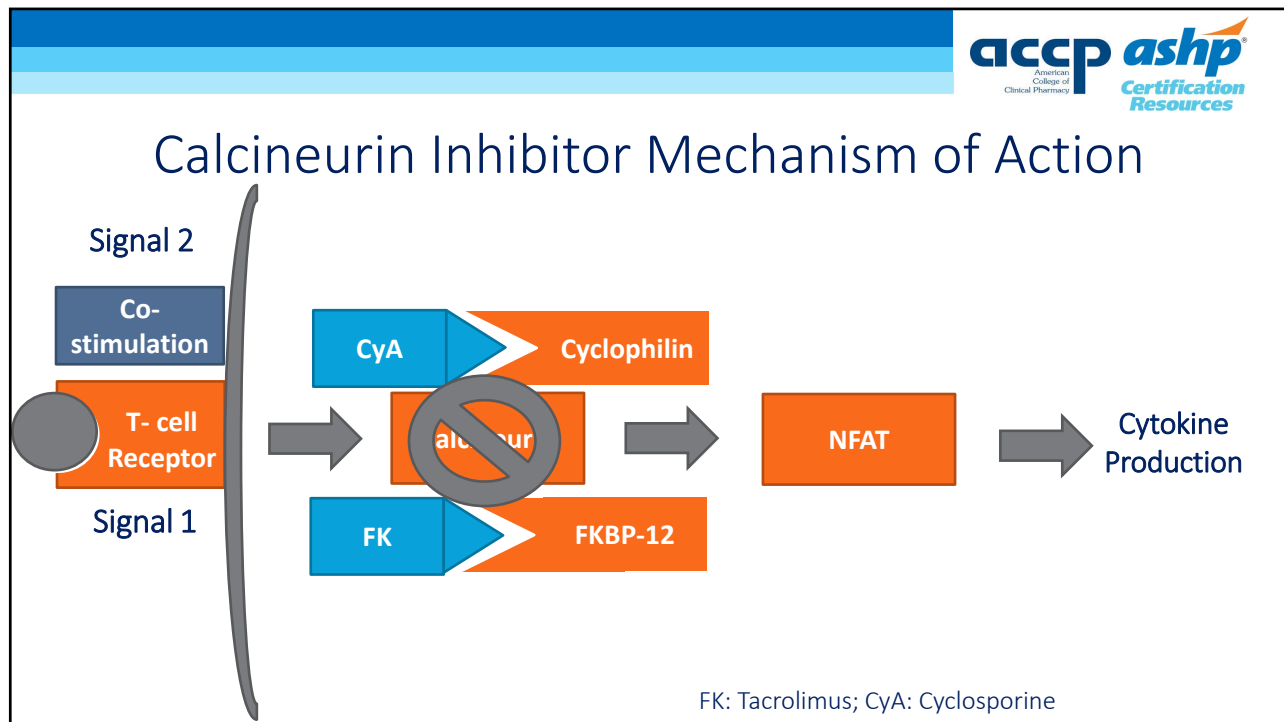
10



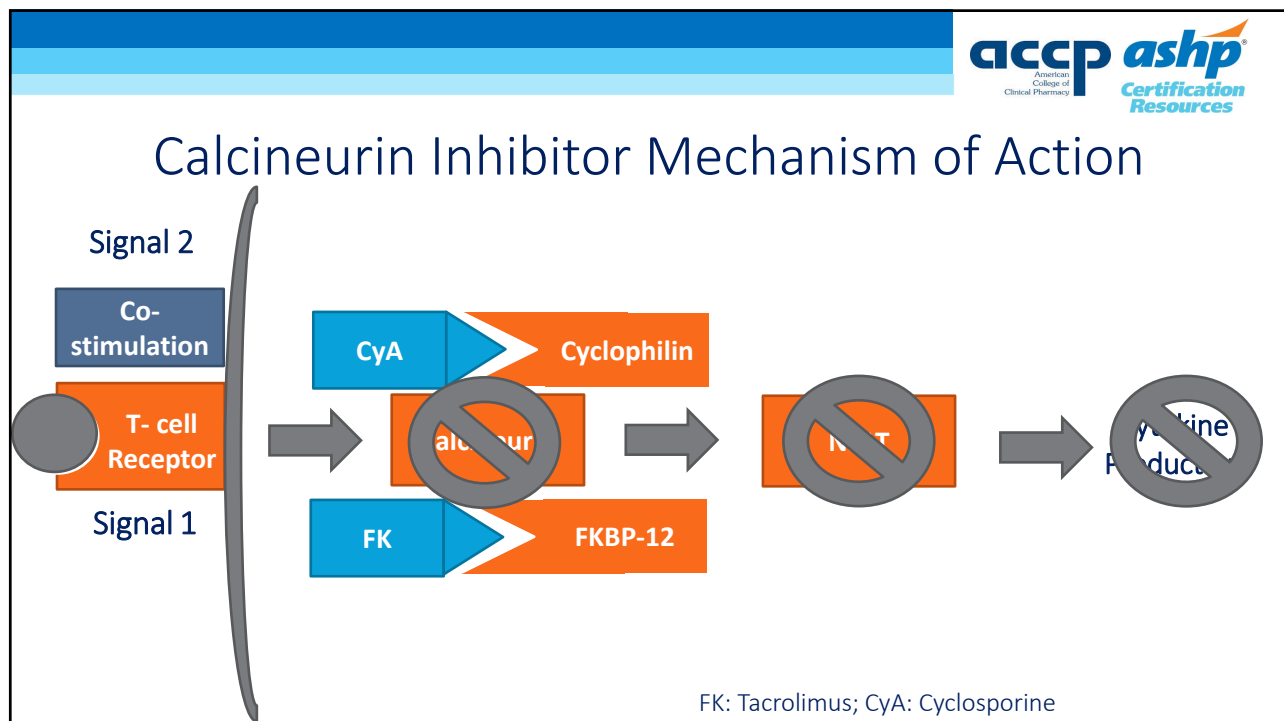
11



12



13



14

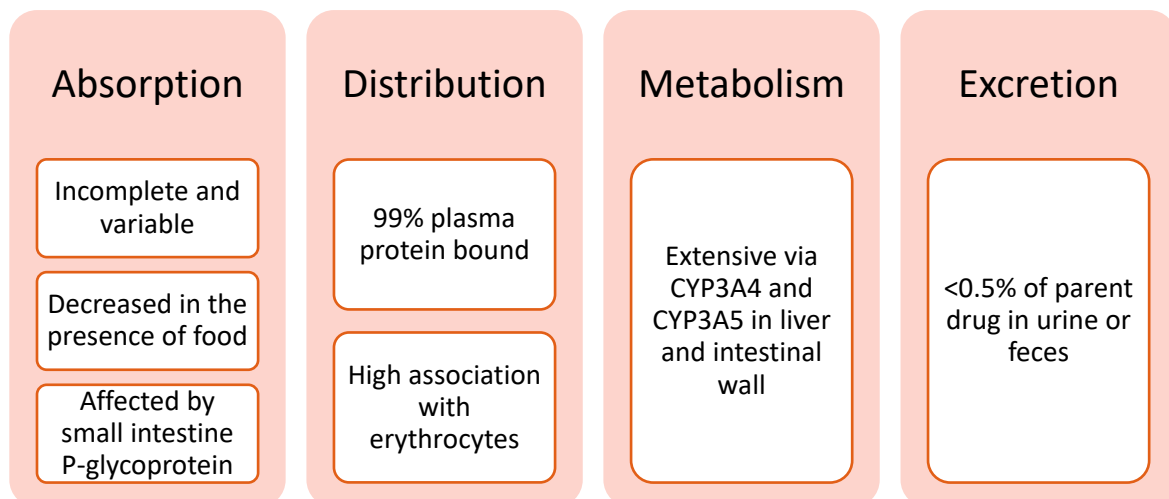
Tacrolimus (Prograf®, FK, FK506)

- FDA Approved Indications
 - Prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic kidney, liver, heart, and lung transplant in combination with other immunosuppressants
- Formulations
 - 0.5 mg, 1 mg, 5 mg capsules
 - Granules for oral suspension (0.2 mg or 1 mg packets)
 - Injection for intravenous use (5 mg/mL ampule)

Prograf [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2021.

15

Tacrolimus Pharmacokinetics



Prograf [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2019.

16

Once Daily Tacrolimus

- Envarsus XR® (LCP tacrolimus)
 - FDA Approved Indications
 - Prophylaxis of organ rejection in de novo kidney transplant patients or in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants
 - Formulations
 - 0.75 mg, 1 mg, 4 mg extended-release tablets
- Astagraf XL® (ER tacrolimus)
 - FDA Approved Indications
 - Prophylaxis of organ rejection in adult and pediatric kidney transplants patients in combination with other immunosuppressants
 - Formulations:
 - 0.5 mg, 1 mg, 5 mg extended-release capsules

Astagraf XL [package insert]. Envarsus XR [package insert].

17

Comparison of Tacrolimus Formulations (ASTCOFF Results)

Drug Formulation	Tmax (hours)	AUC ₀₋₂₄ (h*ng/mL)	Fluctuation (%)	Cmin (ng/mL)	Cmax (ng/mL)
IR Tacrolimus	1.5 (0.9, 20.0)	176.5 ± 50.8	112.6 ± (53.1)	6.1 ± 1.7	14.5 ± 5.5
ER Tacrolimus	1.9 (0.9, 5.9)	165.0 ± 50.0	118.9 ± (48.4)	5.1 ± 1.8	13.2 ± 4.4
LCP Tacrolimus	5.9 (1.5, 14.0)	213.4 ± 83.1	83.6 ± (51.7)	6.8 ± 2.9	13.9 ± 5.3

Am J Transplant. 2017;17(2):432-442.

18

Tacrolimus Dosing

	IR Tacrolimus	ER Tacrolimus	LCP Tacrolimus
Starting dose ^b	0.075-0.2 mg/kg/day in two doses	0.15-0.2 mg/kg/day	0.14 mg/kg/day
Dose conversion from IR tacrolimus ^b	-----	100% IR daily dose	80% IR daily dose
ASTCOFF recommendations	-----	108% IR daily dose	70% IR daily dose
Administration	- Consistently with or without food - Every 12 hours	- Empty stomach ^a - Every 24 hours	- Empty stomach ^a - Every 24 hours

^aEmpty stomach defined as 1 hour before or at least 2 hours after a meal, preferably in the morning

^bper package labeling

Am J Transplant. 2017;17(2):432-442. Ther Drug Monit. 2012;34(1):46-52.
 Prograf [package insert]. Astagraf XL [package insert]. Envarsus XR [package insert].

19

IR VS LCP Tacrolimus: Outcomes

	Bunnapradist et al. 2013		Budde et al. 2014	
Patient Population	326 kidney transplant recipients >3 months to 5 years		543 <i>de novo</i> kidney transplant recipients	
Trial Design	12 month, multicenter, open-label, Phase III RCT		12 month, multicenter, double-blind, Phase III RCT	
Intervention	Converted to LCP-tacro	Remain on IR-tacro	LCP-tacro	IR-tacro
Primary Outcome	Treatment Failure (2.5% vs 2.5%)		Treatment Failure (18.3% vs 19.6%)	
Conclusion	Noninferior (upper 95% CI of treatment difference +4.21%)		Noninferior (upper 95% CI of treatment difference +5.27%)	

Treatment Failure defined as death, graft failure, biopsy proven acute rejection, or lost to follow-up.

Am J Transplant. 2013;13(3):760-9. Am J Transplant. 2014;14(12):2796-806.

20

IR VS LCP Tacrolimus: Neurotoxicities

- Tremors are a common adverse effect of tacrolimus
 - Most pronounced at peak serum concentrations

Switching Study of Kidney Transplant Patients with Tremor to LCP-Tacro (STRATO) Trial

Open label, prospective study of 40 renal transplant patients >1 month to 5 years with a clinically significant tremor	Found reduction in Fahn-Tolosa-Marin (FTM) total tremor score by 5.35 after switch from IR to LCP-tacrolimus at 7 days	Patients reported an improvement of “much better” (23.7%) or “a little better” (55.3%) after switching to LCP-tacrolimus (P<0.0005)
--	--	---

Clin Transplant. 2015;29(9):796-805.

21

Tacrolimus Pharmacogenomics

- Tacrolimus is extensively metabolized by 3A5 in intestine and liver
- CYP3A5 activity is genetically determined
 - Functional allele: *1
 - Non-function alleles: *3, *6, *7
- 80-85% Caucasians are poor metabolizers (two loss of function alleles)
- *1 allele frequencies
 - 50% of African Americans
 - 25-30% Asians
 - 17% Latinos

Clin Pharmacol Ther. 2015;98(1):19-24.

22

CPIC Tacrolimus Dosing Recommendations

Phenotype	Genotype	Example Diplotype	Implication	Starting Dose Recommendation	Strength of Evidence
Extensive metabolizer	Two functional alleles	*1/*1	↓ dose-adjusted trough levels	1.5-2x standard dose (Not to exceed 0.3mg/kg/day)	Strong
Intermediate metabolizer	One functional and one non-functional allele	*1/*3, *1/*6, *1/*7	↓ dose-adjusted trough levels	1.5-2x standard dose (Not to exceed 0.3mg/kg/day)	Strong
Poor metabolizer	Two non-functional alleles	*3/*3, *6/*6, *3/*7	↑ or “normal” dose-adjusted trough levels	Use standard dose	Strong

Clin Pharmacol Ther. 2015;98(1):19-24.

23

IR vs LCP Tacrolimus: Pharmacogenomics

- ASERTAA Study
 - Randomized prospective cross-over study between IR tacrolimus and LCP tacrolimus in 50 African American kidney transplant recipients >6 months
 - LCP tacrolimus dose given was 85% of IR tacrolimus dose
 - No differences in AUC₀₋₂₄ or Cmin between CYP 3A5 expressers and non-expressers
 - Cmax 33% higher in CYP3A5 expressers (p=0.04), only 11% with LCP tacrolimus (p=0.4)

	CYP 3A5 Expresser (n=35)		CYP3A5 Nonexpresser (n=11)	
	LCP Tacro	IR Tacro	LCP Tacro	IR Tacro
AUC ₀₋₂₄ (h*ng/mL)	256.6 (34.9)	230.3 (26.5)	253.4 (42)	215.6 (47.5)
Cmax (ng/mL)	17.3 (39)	25.5 (37.4)	16.5 (45.4)	19.5 (47.3)
Cmin (ng/mL)	7.2 (34.9)	6.5 (27.9)	7.8 (48.1)	6.4 (48.2)

Data presented as geometric mean (% geometric coefficient of variation)

Am J Kidney Dis. 2018;71(3):315-326.

24

Patient Case 1

A patient has been called for a kidney transplant. You review the pharmacogenomic data in the patient's chart that was drawn during evaluation. Their CYP 3A5 alleles are *1/*6. What recommendation could you make based on these results according to the CPIC guidelines?

- A. Start at a higher tacrolimus dose since the patient is an intermediate metabolizer
- B. Use the standard protocol starting dose since the patient is an intermediate metabolizer
- C. Start at a lower tacrolimus dose since the patient is a poor metabolizer
- D. Use cyclosporine instead of tacrolimus since the patient is a hypermetabolizer and will be unable to reach therapeutic concentrations

BPS Outline Domain 1- 3m; Learning Objective 3

25

Patient Case 1

A patient has been called for a kidney transplant. You review the pharmacogenomic data in the patient's chart that was drawn during evaluation. Their CYP 3A5 alleles are *1/*6. What recommendation could you make based on these results according to the CPIC guidelines?

- A. **Start at a higher tacrolimus dose since the patient is an intermediate metabolizer**
- B. Use the standard protocol starting dose since the patient is an intermediate metabolizer
- C. Start at a lower tacrolimus dose since the patient is a poor metabolizer
- D. Use cyclosporine instead of tacrolimus since the patient is a hypermetabolizer and will be unable to reach therapeutic concentrations

BPS Outline Domain 1- 3m; Learning Objective 3

26

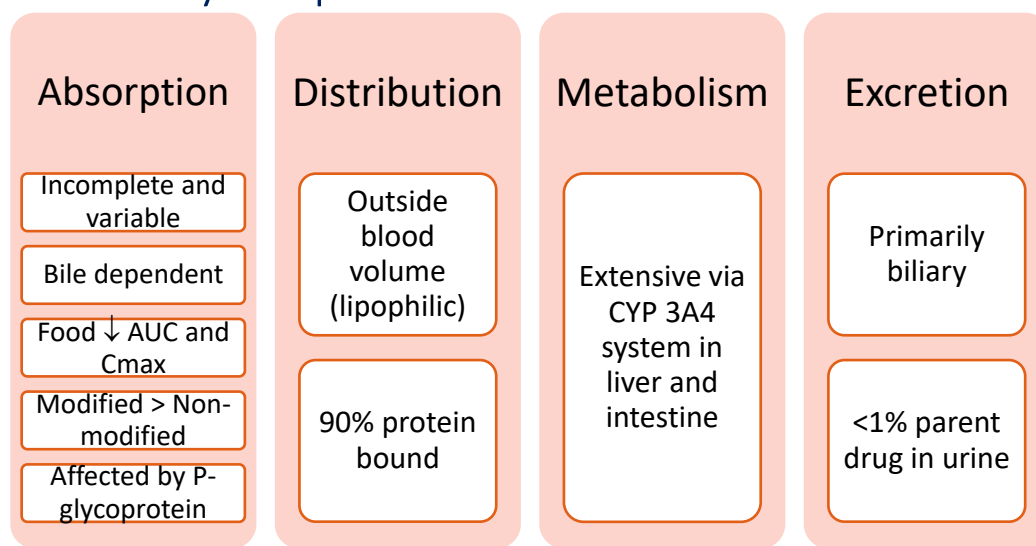
Cyclosporine

- FDA Approved Indications
 - Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants (in combination with azathioprine and corticosteroids)
- Formulations
 - Modified
 - Neoral® and Gengraf®
 - 25 mg, 100 mg gelatin capsules
 - 100 mg/mL oral solution
 - Non-Modified
 - Sandimmune®
 - 25 mg, 100 mg soft gelatin capsules
 - 100 mg/mL oral solution
 - Injection for intravenous use (50 mg/mL ampule)

Neoral [package insert]. Gengraf [package insert]. Sandimmune [package insert].

27

Cyclosporine Pharmacokinetics



Neoral [package insert].

28

Cyclosporine Dosing

- Starting dose: 7-9 mg/kg/day per package labeling
 - In two divided doses, every 12 hours
 - Consistently with or without food
- Conversion from non-modified to modified cyclosporine
 - The two formulations are NOT bioequivalent
 - 1:1 dose ratio
 - Requires increased monitoring to prevent subtherapeutic cyclosporine levels

Neoral [package insert].

29

CNI Therapeutic Drug Monitoring (TDM)

- Why?
 - Narrow therapeutic index
 - Large inter- and intra- patient pharmacokinetic variability
 - High number of drug interactions
- Trough Concentrations (whole blood)
 - Correlates with AUC (FK>Cyclo)
 - IR formulations: drawn 10-14 hours post dose
 - Once daily formulations: drawn 21-27 hours post dose

PK Parameter	Correlation Coefficient with AUC
FK Cmin	> 0.8
Cyclo C2	0.945
Cyclo Cmin	0.53

Transplant Proc 31: 296–298, 1999; Am J Health Syst Pharm. 2012;69(22):1961-75. J Clin Pharmacol. 2018 Jul; 58(7): 891–896.
 Prograf [package insert]. Transplantation. 1996;62(12):1744-52. Am J Transplant. 2009;9 Suppl 3:S1-155.

30

CNI TDM Goals

- Varied depending on patient's immunologic risk, time from transplant, adverse effects, concomitant immunosuppression and institution-specific practices
 - Evidence based regimens will be covered in "Maintenance of Immunosuppression Part Two" Lecture of this series
- General ranges:
 - Tacrolimus: 5-15 ng/mL
 - Cyclosporine: 100-300 ng/mL

31

Cyclosporine C2 Monitoring

- Cyclosporine, modified absorption during the first 4 hours post-dose represents the period of greatest variability
 - C2 is the best single time-point predictor of cyclosporine AUC_{0-4}
- Lack of high quality evidence comparing clinical outcomes of C0 versus C2 monitoring
- C2 Level Goal: 800-1500 ng/mL
 - Level should be drawn within 15 minutes before or after 2 hour time point
- Not universally adopted into routine clinical practice

Transplantation. 2002;73(9 Suppl):S12-8.
 Clin J Am Soc Nephrol. 2007;2(2):374-84.
 Transplantation. 2007;83(12):1525-35.
 Am J Health Syst Pharm. 2012;69(22):1961-75

32

CNI TDM Frequency

- Levels should be monitored according to clinical parameters including but not limited to the following:
 - Frequently with initial start of the medication
 - After any dose adjustment
 - With initiation or discontinuation of interacting medication
 - After change in medication formulation or administration route
 - With change in graft function or sign of rejection
 - With signs or symptoms of toxicity
 - With changes in patient condition including diarrhea or liver injury

Medication	Average half life (hours)	Approx. Steady state (days)
IR tacrolimus	12-18	2.5
LCP tacrolimus	31	7
ER tacrolimus	38	7
cyclosporine	8	2

Values for comparison only. Wide interpatient variability seen in clinical practice.

Clin J Am Soc Nephrol. 2007;2(2):374-84. Astagraf XL [package insert]. Envarsus XR [package insert].

33

Intravenous Calcineurin Inhibitors

Generally avoided due to toxicities

- Anaphylaxis
- Increased nephrotoxicity
- Increased neurotoxicity

Dose Conversions

- Tacrolimus IV:PO 1:5 (can also use 1:4 and 1:3)
- Cyclosporine IV:PO 1:3
- First dose of oral formulation should be given 8-12 hours after stopping IV infusion

Administration logistics

- Non-PVC tubing required to prevent phthalate stripping by castor oil vehicle and to minimize drug adsorption
- Infused as a continuous infusion or in two divided doses over 4 hours

Sandimmune [package insert]; Prograf [package insert]; Am J Health Syst Pharm. 2012;69(22):1961-75.

34

TDM for Intravenous CNIs

- Levels should be drawn from a separate lumen or line than where drug is being infused
- Levels drawn with continuous infusion do not directly correlate to true trough levels with oral formulations
 - Steady state infusion versus peak/troughs
- Lack of consensus on target goals that would represent similar AUCs
- Proposed formula from Nakamura et al.
 - Tacrolimus $C_{ss} = C_{TL} \times 1.4$
 - Cyclosporine $C_{ss} = C_{TL} \times 2.55$

C_{ss} : Concentration during continuous intravenous infusion; C_{TL} : Trough levels with oral administration

Prograf [package insert].
Transplant Proc. 2005;37(4):1725-7.

35

Sublingual Tacrolimus

- Bypasses first pass metabolism as well as gastrointestinal P-glycoprotein and CYP3A4/5
- Avoids intravenous tacrolimus administration when oral route is not feasible or issues with GI tract absorption
- Most common dose conversion is 2 mg oral to 1 mg sublingual
 - 1:1 to 1:4 reported in literature
- Administration Techniques
 - Use of compounded suspension
 - IR capsules opened and administered all at once
 - IR capsules opened and administered one at a time
- Requires hazardous medication handling

Pharmacotherapy. 2014;34(11):1209-19.

36

Patient Case 2

NW is a 62yo female s/p DDRT 5 years ago who presents to the ED with a fever and altered mental status. Her home immunosuppression medications include tacrolimus 4 mg PO every 12 hours, mycophenolate mofetil 1000mg PO every 12 hours, and prednisone 5 mg PO once daily. Her last tacrolimus level in clinic was therapeutic. She is not on any other interacting medication.

She is unable to swallow and the team is requesting you change all her immunosuppression to alternative routes. Which is the best recommendation on how to administer her tacrolimus?

- A. Tacrolimus IV 3 mg/day as continuous infusion
- B. Tacrolimus IV 2 mg/day as continuous infusion
- C. Tacrolimus 2 mg SL every 12 hours
- D. Tacrolimus 1 mg SL every 12 hours

BPS Outline Doman 1 – 2i, Learning Objective 1

37

Patient Case 2

NW is a 62yo female s/p DDRT 5 years ago who presents to the ED with a fever and altered mental status. Her home immunosuppression medications include tacrolimus 4 mg PO every 12 hours, mycophenolate mofetil 1000mg PO every 12 hours, and prednisone 5 mg PO once daily. Her last tacrolimus level in clinic was therapeutic. She is not on any other interacting medication.

She is unable to swallow and the team is requesting you change all her immunosuppression to alternative routes. Which is the best recommendation on how to administer her tacrolimus?

- A. Tacrolimus IV 3 mg/day as continuous infusion
- B. Tacrolimus IV 2 mg/day as continuous infusion
- C. Tacrolimus 2 mg SL every 12 hours
- D. Tacrolimus 1 mg SL every 12 hours

BPS Outline Doman 1 – 2i, Learning Objective 1

38

CNI Adverse Effects

Tacrolimus Only

- Alopecia
- QT prolongation

Both

- Nephrotoxicity
- Dyslipidemia[#]
- Hypertension
- Neurotoxicity^{*}
- Diabetes^{*}
- Hyperkalemia
- Hypomagnesemia

Cyclosporine Only

- Gingival Hyperplasia
- Hirsutism

^{*}Incidence higher with tacrolimus

[#]Incidence higher with cyclosporine

39

CNI Metabolism and Transport

- Mild CYP 3A4 inhibitor
- P-glycoprotein Inhibitor
- OATP and BCRP Inhibitor

- CYP 3A4 substrate
- P-glycoprotein substrate

Cyclosporine

Tacrolimus

Prograf [package insert]. Neoral [package insert].

40

CNI Drug Interactions: 3A4 Inhibitors*

- Grapefruit or grapefruit juice, pomelo
- Protease Inhibitors
- Azole antifungals
- Macrolide antibiotics (erythromycin, clarithromycin)
- Letermovir
- Non-dihydropyridine calcium channel blockers
- Amiodarone/Dronedarone

*List is not all inclusive

Prograf [package insert]. Neoral [package insert]. Nephrology (Carlton). 2008;13(4):337-47.

41

Azole Antifungal and CNI Interactions

Azole	Recommended Dose Reduction	
	Cyclosporine	Tacrolimus
Fluconazole ≥ 200 mg/day	↓ 21-50%	↓ 40%
Itraconazole	↓ 50-60%	↓ 50-60 %
Voriconazole	↓ 50 %	↓ 66%
Posaconazole	↓ 75%	↓ 66%
Ketoconazole	↓ 70-80%	↓ 50-60%
Isavuconazole ^a	↓ 25-30%	↓ 20-25%
Clotrimazole ^a	n/a	↓ 50%

a: based on PK data; reports of clinical experience vary

Pharmacotherapy. 2010;30(8):842-54. Pharmacotherapy. 2006;26(12):1730-44.
 Clin Pharmacol Drug Dev. 2017;6(1):76-85. Ther Drug Monit. 2005;27(5):587-91.

42

CNI Drug Interactions: 3A4 Inducers*

- Rifampin/rifabutin
- Anti-convulsants (phenytoin, carbamazepine, phenobarbital)
- St Johns Wort

*List is not all inclusive

43

CNI Drug Interactions: P-glycoprotein*

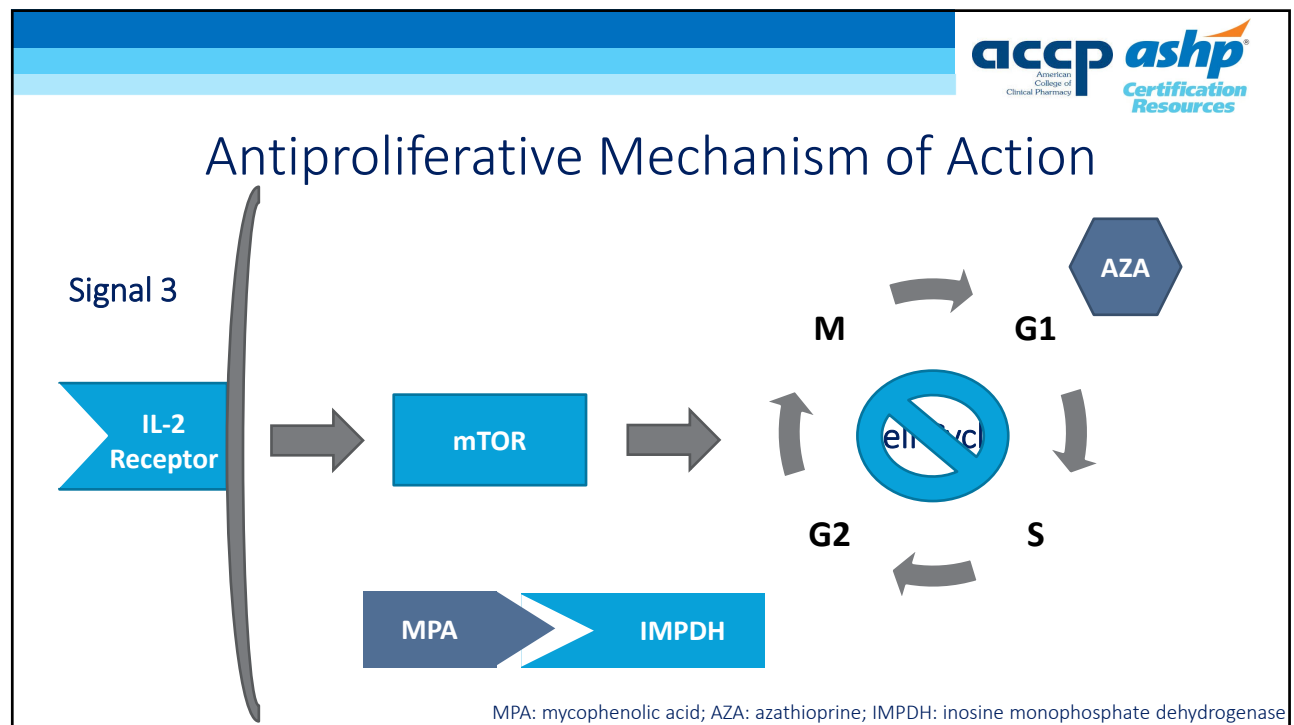
- Cyclosporine INCREASES concentrations of other p-glycoprotein substrates
 - Digoxin
 - Colchicine
 - Statins (concentrations also affected by OATP and BCRP inhibition)
 - Sirolimus/everolimus

*List is not all inclusive

44

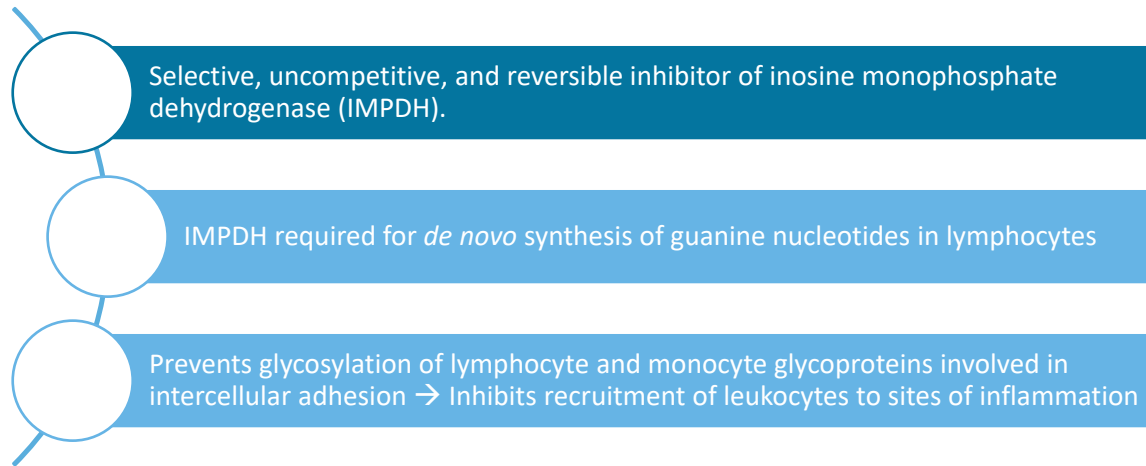
Antiproliferatives

45



46

Mycophenolate Mechanism of Action



Cellcept [package insert].

47

Mycophenolate mofetil (Cellcept[®], MMF)

- FDA Approved Indications
 - Prophylaxis of organ rejection in recipients of allogeneic kidney, heart, or liver transplants, in combination with other immunosuppressants
- Formulations
 - 250 mg capsules
 - 500 mg tablets
 - 200 mg/mL oral suspension
 - Injection for intravenous use (500 mg single-dose vial for reconstitution)

Cellcept [package insert].

48

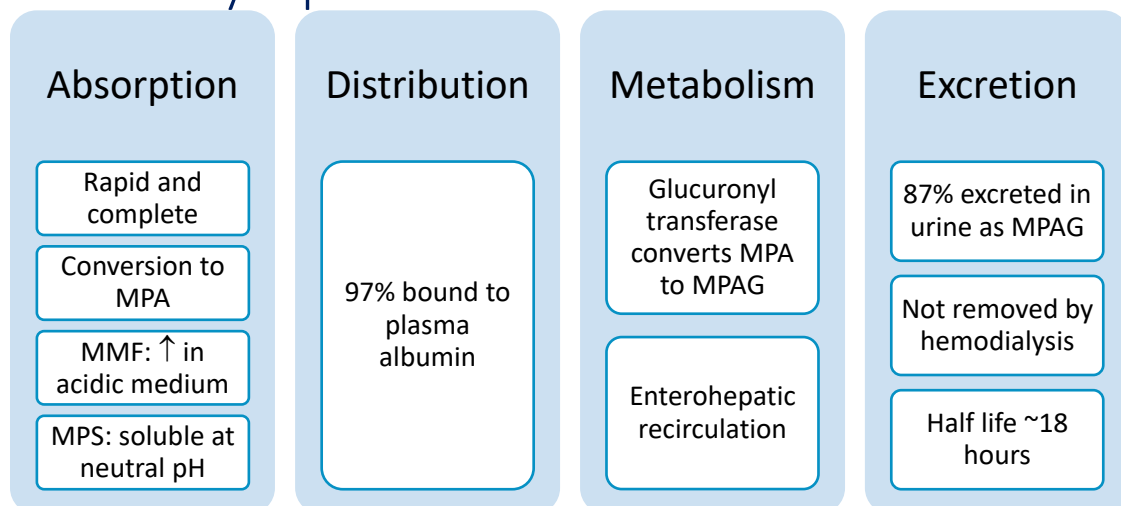
Mycophenolic acid delayed-release (Myfortic[®], MPS)

- FDA Approved Indications
 - Prophylaxis of organ rejection in adult patients receiving a kidney transplant
 - Prophylaxis of organ rejection in pediatric patients 5 years of age and older who are at least 6 months post kidney transplant
 - in combination with cyclosporine and corticosteroids
- Formulations
 - 180 mg, 360 mg delayed-release enteric coated tablets

Myfortic [package insert].

49

Mycophenolate Pharmacokinetics

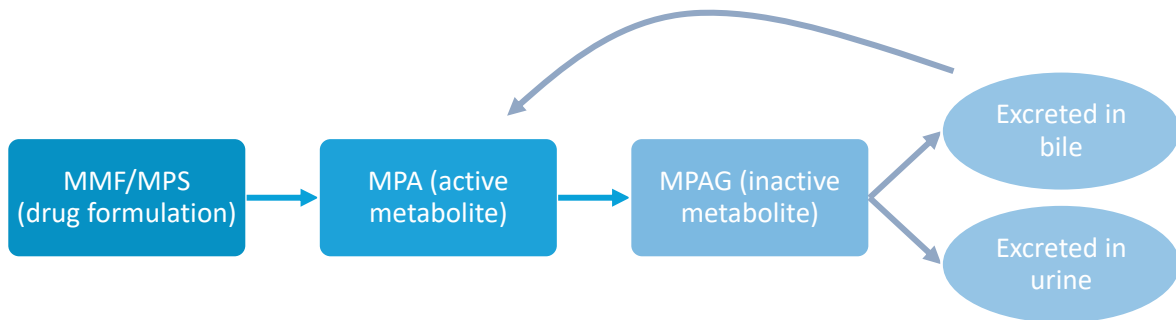


MPA: mycophenolic acid; MPAG: mycophenolic acid glucuronide

Cellcept [package insert]. Myfortic [package insert].

50

MPA/MPAG Enterohepatic Recirculation



MPA: mycophenolic acid; MPAG: mycophenolic acid glucuronide

Cellcept [package insert].

51

Mycophenolate Dosing

- Suggested starting dose
 - MMF: 1000 mg - 1500 mg PO twice daily
 - MPS: 720 mg PO twice daily
- Pediatric dosing
 - MMF: 600 mg/m² PO twice daily
 - MPS: 400 mg/m² PO twice daily

1000 mg
MMF

=

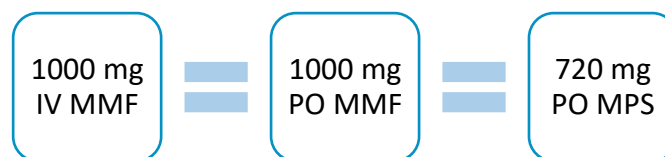
720 mg
MPS

Cellcept [package insert]. Myfortic [package insert].

52

Intravenous Mycophenolate

- 1:1 IV to PO conversion based on MMF dose equivalent
- IV formulation incompatible with other IV solutions
- Infuse over a period of no less than 2 hours



Cellcept [package insert].

53

Mycophenolate Adverse Effects

- Myelosuppression
 - Reduce or interrupt dosing if ANC<1300
 - Recommended monitoring: weekly for first month, twice monthly for second and third month, then monthly for remainder of first year
- Gastrointestinal
 - Includes nausea, vomiting, and diarrhea
 - Usually responsive to dose reduction
 - Colitis can be diagnosed with biopsy
 - Possible with both intravenous and oral formulations
- Teratogenicity
 - Discussed in “Transplant Resources and Patient Education” Lecture

Cellcept [package insert]. Clin Transplant. 2000;14(3):179-88. Mod Pathol. 2009;22(6):737-43.

54

MMF vs MPS

	Budde et al. 2004		Langone et al. 2011	
Patient Population	322 stable kidney transplant recipients >6 months from transplant		396 kidney transplant recipients with GI symptoms >4 weeks from transplant	
Trial Design	12 month, multicenter, double-blind RCT		4 week, multicenter, double-blind RCT	
Intervention	Continue MMF 1 g BID	Converted to MPS 720 mg BID	Continue MMF dose	Equivalent MPS dose
Results	No difference GI adverse effects -3 months (20.9% vs 26.4%) -12 months (24.5% vs 29.6%)		Greater decrease in Gastrointestinal Symptom Rating Scale score (-0.2 vs -0.3, p=0.026)	

Am J Transplant. 2004;4(2):237-43. Transplantation. 2011;91(4):470-8.

55

MPA Therapeutic Drug Monitoring

- Routine use is NOT recommended
- A limited sample strategy is preferred versus a single concentration time point
 - Better estimation of AUC given complex pharmacokinetics
 - Some data suggests an association with early post-operative efficacy
 - Unclear data on association with drug-related toxicity
- Use in target populations may provide the most benefit
 - High immunologic risk
 - Minimization or withdrawal of immunosuppression
 - Altered renal, hepatic, or bowel function

TDM Targets	AUC (mg x hr/L)	Trough (mg/L)
Renal	30-60	With Cya: ≥ 1.3 With FK: ≥ 1.9
Liver, Bowel, Pancreas	-----	1-3.5
Thoracic	-----	With FK: $>2-3$
Pediatric	30-60	1-3.5

- Cystic fibrosis
- Drug interactions
- Noncompliance

Clin J Am Soc Nephrol. 2010;5(2):341-58.

56

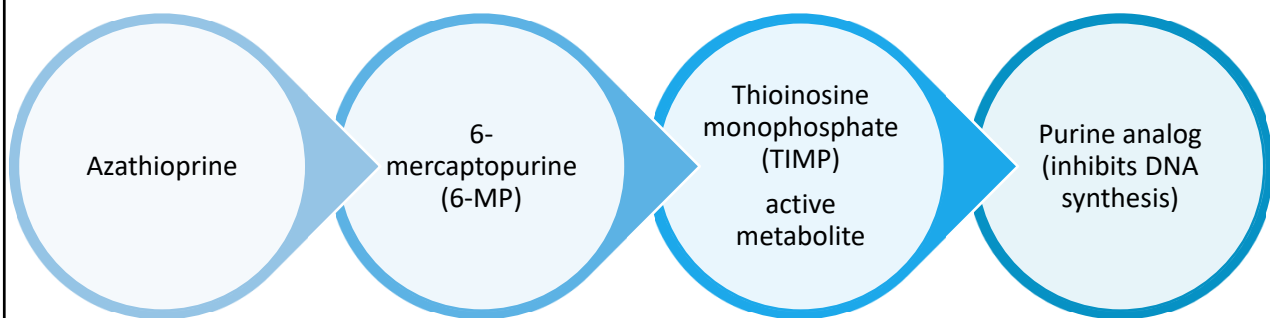
Drug Interactions Affecting Mycophenolate

Interaction		Recommendation
Decreased MPA absorption	Antacids (Mg or Al)	Give 2 hours after mycophenolate
	Proton pump inhibitors (MMF only)	Monitor for alterations in efficacy
Interference with enterohepatic circulation	Cyclosporine	Monitor for alterations in efficacy
	Antimicrobials eliminating beta-glucuronidase-producing bacteria in the intestine	Monitor for alterations in efficacy
	Sevelamer	Give 2 hours after mycophenolate
	Bile acid sequestrants (cholestyramine)	Avoid use
Effect on glucuronidation	Telmisartan (inducer)	Monitor for alterations in efficacy
	Isavuconazole (inhibitor)	Monitor for alterations in efficacy

Cellcept [package insert]. Myfortic [package insert].

57

Azathioprine Mechanism of Action



Imuran [package insert].

58

Azathioprine

- FDA Approved Indications
 - An adjunct for the prevention of rejection in renal transplantation
- Formulations
 - 50 mg tablets (Imuran®, generic)
 - 75 mg, 100 mg tablets (Azasan®)
 - Injection for intravenous use (100 mg vial)

Imuran [package insert]. Azathioprine sodium for injection [package insert]. Azasan [package insert].

59

Azathioprine Pharmacokinetics

Absorption

Well absorbed

Distribution

Highly distributed into tissues

Moderate protein binding

Metabolism

Rapidly converted to 6-MP and other metabolites

Excretion

Metabolites renally cleared

Imuran [package insert].

60

Azathioprine Dosing

3-5 mg/kg once daily as primary immunosuppressant

1-3 mg/kg once daily as maintenance therapy

Intravenous formulation usually given over 30-60 minutes

IV:PO 1:1 conversion ratio

Partially dialyzable

Imuran [package insert].

61

Azathioprine Adverse Effects

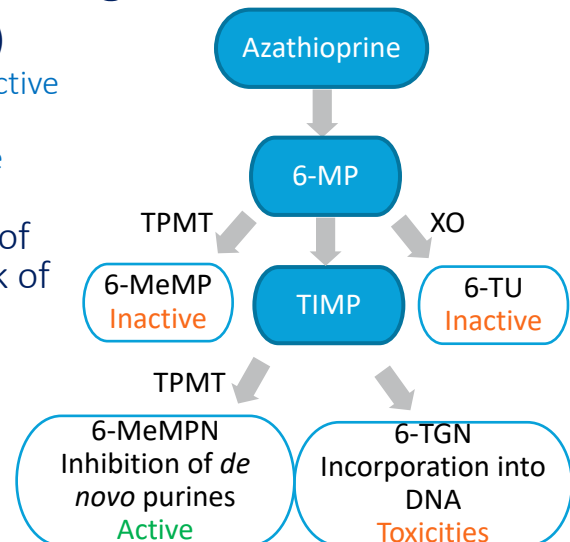
- Myelosuppression
 - Dose related and resolves 7-10 days with dose reduction
 - Monitoring recommendations: CBC weekly during the first month, twice monthly for the second and third months, then monthly
- Nausea and vomiting
- Pancreatitis (rare)
- Hepatotoxicity (rare)

Imuran [package insert].

62

Azathioprine Pharmacogenomics

- Thiopurine methyltransferase (TPMT)
 - Catabolizes 6-mercaptopurine to an inactive methylmercaptopurine base
 - Methylates thioinosine monophosphate (TIMP)
- Lack of TPMT function → high levels of TGN (thioguanine nucleotides) → risk of life-threatening myelosuppression
- Consideration should be given to genotype patients for TPMT when initiating azathioprine



Clin Pharmacol Ther. 2019;105(5):1095-1105. Imuran [package insert].

63

CPIC Azathioprine Dosing Recommendations

Phenotype	Genotype	Implication	Starting Dose Recommendation	Strength of Evidence
Normal metabolizer	Two normal function alleles	Lower levels of TGN; normal risk of toxicity	Normal starting dose	Strong
Intermediate metabolizer	One normal function allele and one no function allele	Moderate-high level of TGN; increased risk of toxicity	Reduce to 30-80% of normal starting dose	Strong
Poor metabolizer	Two no function alleles	Extremely high level of TGN; fatal toxicity possible	Consider alternative therapy. If necessary reduce by 10-fold and dose 3x weekly	Strong

Clin Pharmacol Ther. 2019;105(5):1095-1105.

64

Azathioprine Drug Interactions

- Xanthine oxidase inhibitors
- Increased risk of myelotoxicity due to reduced azathioprine metabolism

Allopurinol

- Avoid if possible
- Reduce azathioprine dose by at least 67% if given together

Febuxostat

- Contraindicated

Prog Transplant. 2015;25(3):263-70. Uloric [package insert].

65

Patient Case 3

Which monitoring parameter would be most important to check for adverse effects after converting a patient from mycophenolate to azathioprine?

- White count
- Uric acid
- Serum creatinine
- EBV serology

BPS Outline Domain 1- 3g; Learning Objective 6

66

Patient Case 3

Which monitoring parameter would be most important to check for adverse effects after converting a patient from mycophenolate to azathioprine?

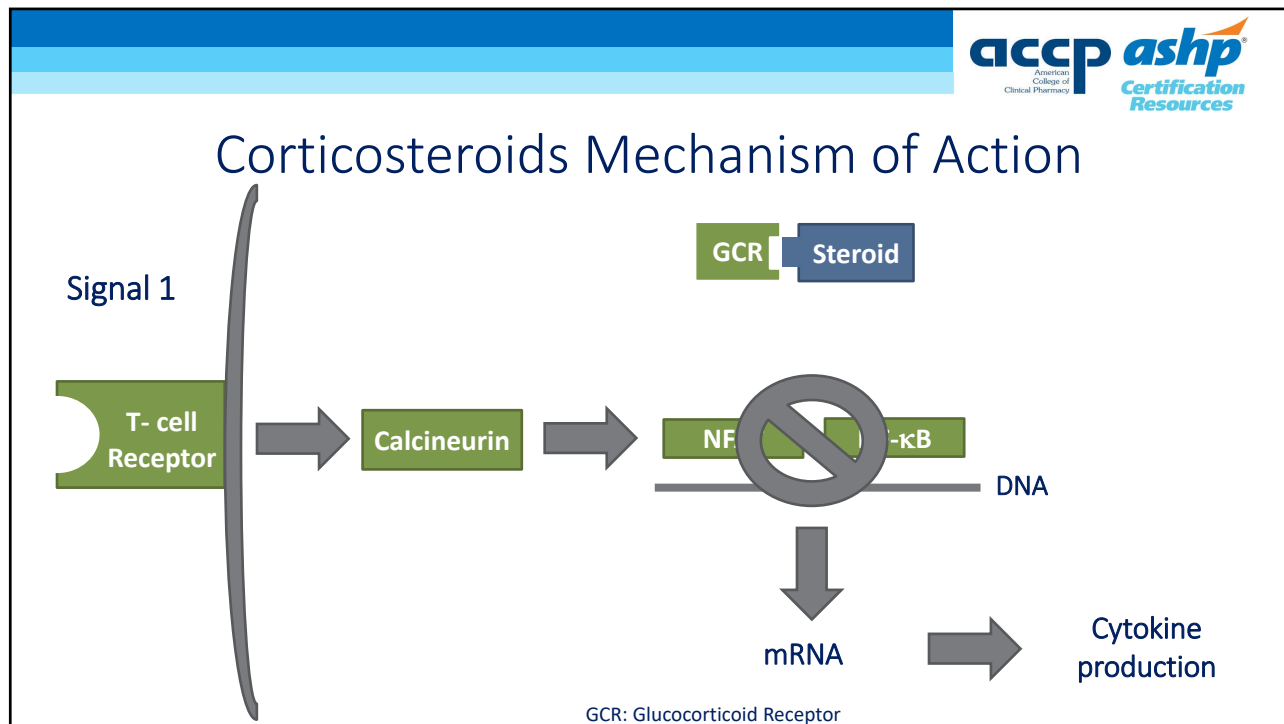
- A. White count
- B. Uric acid
- C. Serum creatinine
- D. EBV serology

BPS Outline Domain 1- 3g; Learning Objective 6

67

Corticosteroids

68



69

accp ashp
American College of Clinical Pharmacy Certification Resources

Glucocorticoids

- Prednisone*
 - 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg tablets
 - 5 mg/5mL oral solution
 - 5 mg/mL oral concentrate
- Methylprednisolone*
 - Solution for injection, as sodium succinate
- Dosing
 - Varies by organ, transplant center, and patient population
 - High doses given in the operating room and tapered over weeks to months
 - Patients can be maintained on a maintenance dose or corticosteroids can be stopped

* Most commonly used agents in transplant

Prednisone [package insert]. SOLU-MEDROL [package insert].

70

Corticosteroid Adverse Effects

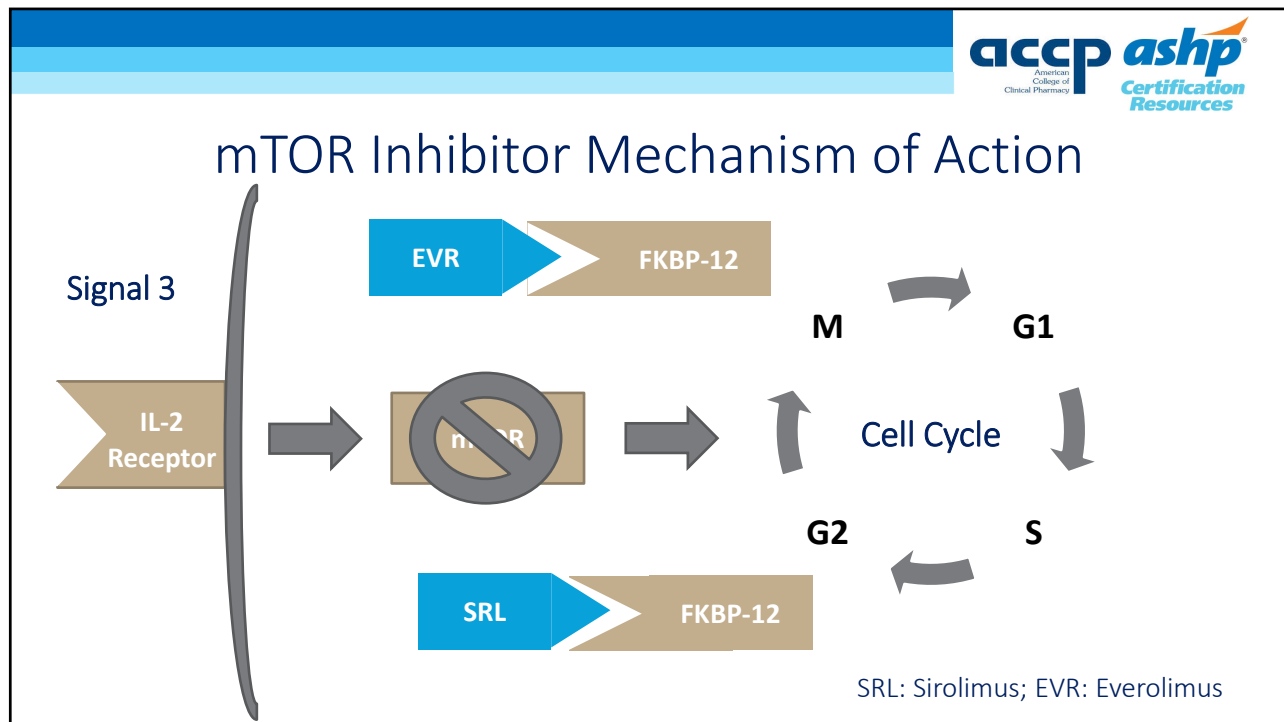
Cosmetic	Psychiatric	Gastro-intestinal	Metabolic	Endocrine	Other
<ul style="list-style-type: none"> • Acne • Skin fragility • Moon face • Buffalo hump • Truncal obesity 	<ul style="list-style-type: none"> • Emotional lability • Insomnia • Anxiety • Depression • Psychosis • Impaired cognition • Memory loss 	<ul style="list-style-type: none"> • Gastric ulcer • Increased appetite • Nausea 	<ul style="list-style-type: none"> • Hyperlipidemia • Salt and water retention • Hypertension • Weight gain • Osteoporosis 	<ul style="list-style-type: none"> • Adrenal insufficiency • Growth suppression in children • Hyperglycemia 	<ul style="list-style-type: none"> • Leukocytosis • Poor wound healing • Proximal myopathy • Cataracts • Glaucoma

Prednisone [package insert].

71

mTOR Inhibitors

72



73

accp ashp
American College of Clinical Pharmacy Certification Resources

Additional mTOR Inhibitor MOA

- Inhibition of growth factors that affect angiogenesis, fibroblast proliferation, and vascular permeability
 - Use in prevention of malignancy
- Inhibition of mTOR mediated signals for proliferation of smooth muscle and endothelial cells
 - Use in cardiac allograft vasculopathy
- Inhibition of viral replication
 - Use in prevention of CMV

Role to be discussed further in lectures on Malignancy, Infection, and Heart Transplant.

Rapamune [package insert]. Zortress [package insert].

74

Sirolimus (Rapamune®)

- FDA Approved Indications
 - Prophylaxis of organ rejection in patients ≥ 13 years receiving renal transplants:
 - Patients at low-to-moderate immunologic risk: Use initially with cyclosporine and corticosteroids. Cyclosporine withdrawal is recommended 2-4 months after transplantation
 - Patient at high immunologic risk: Use in combination with cyclosporine and corticosteroids for the first 12 months following transplantation
- Formulations
 - 0.5 mg, 1 mg, 2 mg tablets
 - 1 mg/mL oral solution

Rapamune [package insert].

75

Everolimus (Zortress®)

- FDA Approved Indications
 - Prophylaxis of organ rejection in adult patients:
 - After kidney transplant: at low-moderate immunologic risk. Use in combination with basiliximab, cyclosporine (reduced doses) and corticosteroids.
 - After liver transplant: Administer no earlier than 30 days posttransplant. Use in combination with tacrolimus (reduced doses) and corticosteroids.
- Formulations
 - 0.25 mg, 0.5 mg, 0.75 mg, 1 mg tablets

Zortress [package insert].

76

mTOR Inhibitor Pharmacokinetics

Absorption	Distribution	Metabolism	Excretion
Bioavailability <30%	74-92% protein bound	Extensive via intestinal and hepatic CYP 3A system	Primary in the feces as inactive metabolites
Tmax 1-2 hours			
Affected by P- glycoprotein			

Rapamune [package insert]. Zortress [package insert].

77

mTOR Inhibitor Dosing

	Sirolimus	Everolimus
Loading dose*	6-15 mg	N/A
Maintenance dose	2-5 mg	0.75-1 mg
Frequency	Every 24 hours	Every 12 hours
Administration	Consistently with or without food	Consistently with or without food
Timing with CNI	Give 4 hours after cyclosporine*	Give at same time

*per package labeling, use in clinical practice is limited

Specific dosing regimens will be discussed in lectures on evidence based regimens.

Am J Health Syst Pharm. 2012;69(22):1961-75. Rapamune [package insert]. Zortress [package insert].

78

mTOR Inhibitor Therapeutic Drug Monitoring

- Why?
 - Narrow therapeutic index
 - High number of drug interactions
- AUC and Cmin well correlated
- Dose adjustments can generally be made based on a simple proportion

	Sirolimus	Everolimus
Half Life (hours)	62	18-35
Approx. steady state (days)	10-14	4-7
Trough Goals (ng/mL)	5-24	3-8

Clin Ther. 2000;22 Suppl B:B101-121.

Rapamune [package insert].

Clin Pharmacokinet. 2004;43(2):83-95.

79

mTORi Adverse Effects

Metabolic	Renal	Hematologic	Gastro-intestinal	Other
<ul style="list-style-type: none"> • Hyperlipidemia • Hypertriglyceridemia • Glucose intolerance 	<ul style="list-style-type: none"> • Nephrotoxicity (particularly with full dose CNI use) • Proteinuria 	<ul style="list-style-type: none"> • Neutropenia • Anemia • Thrombocytopenia 	<ul style="list-style-type: none"> • Stomatitis • Mucositis • Diarrhea 	<ul style="list-style-type: none"> • Delayed wound healing • Lymphocele • Angioedema • Non-infectious pneumonitis • Male infertility • Peripheral edema

Black box warnings exist for mTORi use early post-transplant related to post-operative complications

Rapamune [package insert]. Zortress [package insert].

80

Patient Case 4

BR is a 45yo female s/p OHT 5 years ago. She calls the transplant office to complain about persistent mouth sores that have not resolved in several weeks after treatment by her PCP. You are asked to review her medication list for potential causes. Which medication below is the most likely cause of her mouth sores?

- A. Tacrolimus
- B. Everolimus
- C. Azathioprine
- D. Prednisone

BPS Outline Domain 1- 3g; Learning Objective 5

81

Patient Case 4

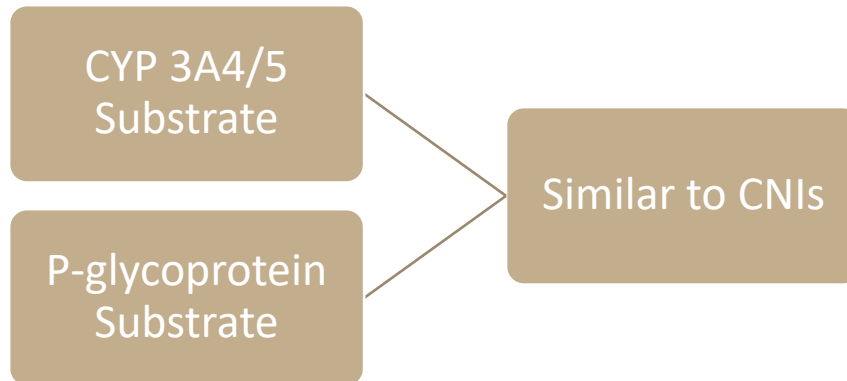
BR is a 45yo female s/p OHT 5 years ago. She calls the transplant office to complain about persistent mouth sores that have not resolved in several weeks after treatment by her PCP. You are asked to review her medication list for potential causes. Which medication below is the most likely cause of her mouth sores?

- A. Tacrolimus
- B. **Everolimus**
- C. Azathioprine
- D. Prednisone

BPS Outline Domain 1- 3g; Learning Objective 5

82

mTORi Drug Interactions



83

Patient Case 5

SH is a 45yo female s/p OHT 2 years ago. She was recently diagnosed with aspergillosis and started on voriconazole 250 mg PO BID. Her current immunosuppressive regimen consists of tacrolimus 2.5 mg PO every 12 hours and sirolimus 2 mg PO every 24 hours. The team consults you for dosing and monitoring recommendations. Which is the best response?

- A. No dose adjustments are necessary. Check trough levels within 7 days.
- B. Decrease tacrolimus to 2 mg PO every 12 hours and sirolimus to 1.5 mg PO every 24 hours with first dose of voriconazole. Check trough levels within 2-3 days
- C. Decrease tacrolimus to 1 mg PO every 12 hours and sirolimus to 0.5 mg PO every 24 hours starting 3 days after starting voriconazole. Check trough levels within 7 days.
- D. Decrease tacrolimus to 1 mg PO every 12 hours and sirolimus to 0.5 mg PO every 24 hours with the first dose of voriconazole. Check trough levels within 2-3 days.

BPS Outline Domain 1- 2i, 3g; Learning Objective 4

84

Patient Case 5

SH is a 45yo female s/p OHT 2 years ago. She was recently diagnosed with aspergillosis and started on voriconazole 250 mg PO BID. Her current immunosuppressive regimen consists of tacrolimus 2.5 mg PO every 12 hours and sirolimus 2 mg PO every 24 hours. The team consults you for dosing and monitoring recommendations. Which is the best response?

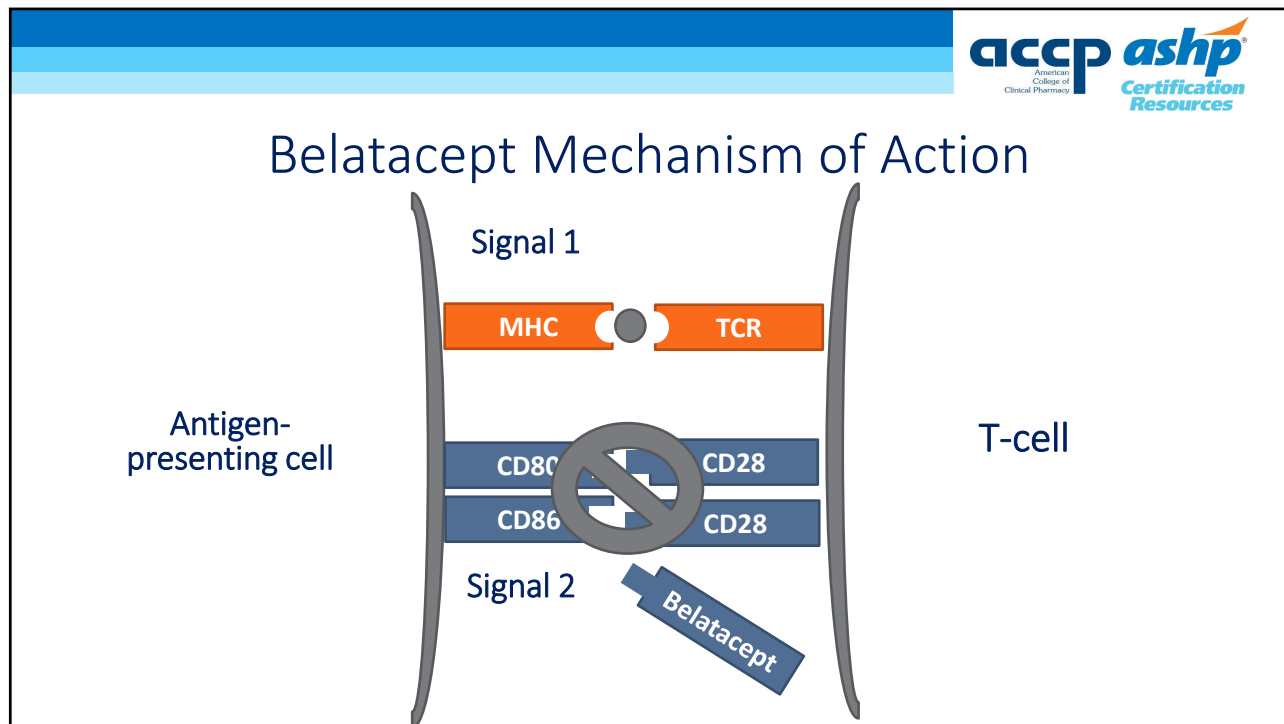
- A. No dose adjustments are necessary. Check trough levels within 7 days.
- B. Decrease tacrolimus to 2 mg PO every 12 hours and sirolimus to 1.5 mg PO every 24 hours with first dose of voriconazole. Check trough levels within 2-3 days
- C. Decrease tacrolimus to 1 mg PO every 12 hours and sirolimus to 0.5 mg PO every 24 hours starting 3 days after starting voriconazole. Check trough levels within 7 days.
- D. **Decrease tacrolimus to 1 mg PO every 12 hours and sirolimus to 0.5 mg PO every 24 hours with the first dose of voriconazole. Check trough levels within 2-3 days.**

BPS Outline Domain 1- 2i, 3g; Learning Objective 4

85

Costimulation Blocker

86



87

accp ashp
American College of Clinical Pharmacy Certification Resources

Belatacept (Nulojix®)

- FDA Approved Indication
 - Prophylaxis of organ rejection in adult patients receiving a kidney transplant in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids
 - Use only in patients who are EBV seropositive
- Formulations
 - Lyophilized powder for injection (250 mg vial)

Nulojix [package insert].

88

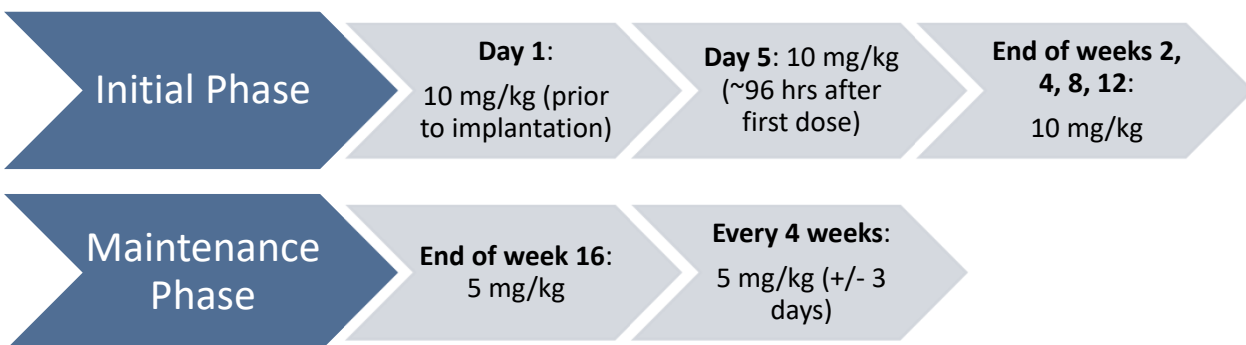
Belatacept Administration

- 30 minute infusion using a sterile, non-pyrogenic low-protein binding filter
- No premedication required
- Dosing considerations
 - Must be evenly divisible by 12.5 mg
 - Use actual body weight at time of transplant
 - Update dosing weight if weight changes by >10%

Nulojix [package insert].

89

Belatacept De Novo Dosing



Nulojix [package insert].

90

accp ashp
American College of Clinical Pharmacy
Certification Resources

Example Belatacept Conversion Dosing

Belatacept Dosing Schedule

The diagram illustrates the Belatacept dosing schedule. It consists of three rows of chevron arrows pointing right. The top row shows dosing at 5 mg/kg on Days 1, 15, 23, 29, 43, and 57, followed by 'Every 4 weeks'. The middle row shows the dosing schedule. The bottom row shows the tapering schedule: 100% on Day 1, 40-60% on Day 15, 20-30% on Day 23, and 'Stop' on Day 29.

CNI Taper Schedule

*Additional dosing regimens to be discussed in Maintenance Part 2 with organ specific evidence-based regimens

Clin J Am Soc Nephrol. 2011;6(2):430-9.

91

accp ashp
American College of Clinical Pharmacy
Certification Resources

Post-Transplant Lymphoproliferative Disorder (PTLD)

The diagram shows three key points about PTLD risk with belatacept, each preceded by a magnifying glass icon. The points are: 1. Black box warning with belatacept due to increase risk of CNS disease. 2. Risk of PTLD was higher in EBV seronegative patients. 3. EBV serology should be obtained prior to starting belatacept and not used for EBV seronegative patients or those with an unknown serostatus.

*Additional information will be discussed in lectures on Malignancy and Patient Education

Nulojix [package insert].

92

Patient Case 6

TW is a 53 yo male s/p renal transplant 8 months ago (92 kg, 69 in). The transplant team would like to convert from his CNI-based regimen to belatacept. What consideration should you include while initiating and monitoring his belatacept therapy?

- A. Use ideal body weight when calculating his dose of belatacept
- B. Update his dosing weight if his weight changes by >5%
- C. Ensure that he is EBV seropositive
- D. Ensure that he is EBV seronegative

BPS Outline Domain 3g; Learning Objective 6

93

Patient Case 6

TW is a 53 yo male s/p renal transplant 8 months ago (92 kg, 69 in). The transplant team would like to convert from his CNI-based regimen to belatacept. What consideration should you include while initiating and monitoring his belatacept therapy?

- A. Use ideal body weight when calculating his dose of belatacept
- B. Update his dosing weight if his weight changes by >5%
- C. Ensure that he is EBV seropositive
- D. Ensure that he is EBV seronegative

BPS Outline Domain 3g; Learning Objective 6

94

Key Takeaways

- Maintenance immunosuppression is a lifelong therapy after solid organ transplant
- Patient specific factors must be considered and addressed to avoid extensive adverse effects
- Vigilant monitoring is necessary for many anti-rejection medications due to narrow therapeutic indices and drug-drug interactions
- Pharmacogenomics can be utilized for several immunosuppressants to improve medication efficacy and prevent life threatening toxicities

95

Maintenance of Immunosuppression Part One

Kimberly Harrison, Pharm.D., BCPS, BCTXP
Cardiothoracic Transplant Clinical Specialist
Vanderbilt University Medical Center
Nashville, Tennessee

96

References

- Astagraf XL [package insert]. Killorglin, Ireland: Astellas Ireland Co., Limited; 2019.
- Azasan [package insert]. Wilmington, NC: Alcam Corporation; 2019.
- Azathioprine sodium for injection [package insert]. Goslar, Germany: Thymoorgan Pharmazie GmbH; 2019.
- Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24.
- Budde K, Bunnapradist S, Grinyo JM, et al. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. Am J Transplant. 2014;14(12):2796-806.
- Budde K, Curtis J, Knoll G, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. Am J Transplant. 2004;4(2):237-43.
- Bunnapradist S, Ciechanowski K, West-thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. Am J Transplant. 2013;13(3):760-9.
- Cellcept [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2019.

97

References

- Dodds-ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010;30(8):842-54.
- Doligalski CT, Liu EC, Sammons CM, Silverman A, Logan AT. Sublingual administration of tacrolimus: current trends and available evidence. Pharmacotherapy. 2014;34(11):1209-19.
- Envarsus XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc; 2018.
- Gengraf® [package insert]. North Chicago, IL: AbbVie Inc.; 2018.
- Groll AH, Desai A, Han D, et al. Pharmacokinetic Assessment of Drug-Drug Interactions of Isavuconazole With the Immunosuppressants Cyclosporine, Mycophenolic Acid, Prednisolone, Sirolimus, and Tacrolimus in Healthy Adults. Clin Pharmacol Drug Dev. 2017;6(1):76-85.
- Imuran [package insert]. Hunt Valley, MD: Pharmaceuticals International, Inc; 2014.
- KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1-155.

98

References

- Keown P, Landsberg D, Halloran P, et al. A randomized, prospective multicenter pharmacoepidemiologic study of cyclosporine microemulsion in stable renal graft recipients. Report of the Canadian Neoral Renal Transplantation Study Group. *Transplantation*. 1996;62(12):1744-52.
- Kirchner GI, Meier-wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet*. 2004;43(2):83-95.
- Knight SR, Morris PJ. The clinical benefits of cyclosporine C2-level monitoring: a systematic review. *Transplantation*. 2007;83(12):1525-35.
- Kuypers DR, Le meur Y, Cantarovich M, et al. Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. *Clin J Am Soc Nephrol*. 2010;5(2):341-58.
- Langone AJ, Chan L, Bolin P, Cooper M. Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. *Transplantation*. 2011;91(4):470-8.

99

References

- Langone A, Steinberg SM, Gedaly R, et al. Switching STudy of Kidney TRansplant PATients with Tremor to LCP-TacRO (STRATO): an open-label, multicenter, prospective phase 3b study. *Clin Transplant*. 2015;29(9):796-805.
- Lee RA, Gabardi S. Current trends in immunosuppressive therapies for renal transplant recipients. *Am J Health Syst Pharm*. 2012;69(22):1961-75.
- Levy G, Thervet E, Lake J, Uchida K. Patient management by Neoral C(2) monitoring: an international consensus statement. *Transplantation*. 2002;73(9 Suppl):S12-8.
- Macdonald A, Scarola J, Burke JT, Zimmerman JJ. Clinical pharmacokinetics and therapeutic drug monitoring of sirolimus. *Clin Ther*. 2000;22 Suppl B:B101-121.
- Myfortic [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
- Nakamura Y, Takeuchi H, Okuyama K, et al. Evaluation of appropriate blood level in continuous intravenous infusion from trough concentrations after oral administration based on area under trough level in tacrolimus and cyclosporine therapy. *Transplant Proc*. 2005;37(4):1725-7.

100

References

- Neoral [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2019.
- Nowack R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John's Wort - and beyond!. Nephrology (Carlton). 2008;13(4):337-47.
- Nulojix [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
- Pescovitz MD, Conti D, Dunn J, et al. Intravenous mycophenolate mofetil: safety, tolerability, and pharmacokinetics. Clin Transplant. 2000;14(3):179-88.
- Philosophe B, Leca N, West-thielke PM, et al. Evaluation of Flexible Tacrolimus Drug Concentration Monitoring Approach in Patients Receiving Extended-Release Once-Daily Tacrolimus Tablets. J Clin Pharmacol. 2018;58(7):891-896.
- Prednisone [package insert]. Eatontown, NJ: West-Ward Pharmaceuticals Corp; 2017.
- Prograf [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2021.
- Rapamune [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals LLC; 2020.

101

References

- Relling MV, Schwab M, Whirl-carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-1105.
- Rostaing L, Massari P, Garcia VD, et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clin J Am Soc Nephrol. 2011;6(2):430-9.
- Saad AH, Depestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy. 2006;26(12):1730-44.
- Sandimmune® [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2019.
- Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. Clin J Am Soc Nephrol. 2007;2(2):374-84.

102

References

- Selbst MK, Ahrens WA, Robert ME, Friedman A, Proctor DD, Jain D. Spectrum of histologic changes in colonic biopsies in patients treated with mycophenolate mofetil. *Mod Pathol*. 2009;22(6):737-43.
- SOLU-MEDROL [package insert]. New York, NY: Pfizer Inc; 2019.
- Sullivan PM, William A, Tichy EM. Hyperuricemia and gout in solid-organ transplant: update in pharmacological management. *Prog Transplant*. 2015;25(3):263-70.
- Tremblay S, Nigro V, Weinberg J, Woodle ES, Alloway RR. A Steady-State Head-to-Head Pharmacokinetic Comparison of All FK-506 (Tacrolimus) Formulations (ASTCOFF): An Open-Label, Prospective, Randomized, Two-Arm, Three-Period Crossover Study. *Am J Transplant*. 2017;17(2):432-442.
- Trofe-clark J, Brennan DC, West-thielke P, et al. Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients. *Am J Kidney Dis*. 2018;71(3):315-326.
- Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2019.

103

References

- Undre NA, van Hooff J, Christiaans M, et al. Low systemic exposure to tacrolimus correlates with acute rejection. *Transplant Proc*. 1999; 31:296 –298.
- Van hooff J, Van der walt I, Kallmeyer J, et al. Pharmacokinetics in stable kidney transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. *Ther Drug Monit*. 2012;34(1):46-52.
- Vasquez EM, Shin GP, Sifontis N, Benedetti E. Concomitant clotrimazole therapy more than doubles the relative oral bioavailability of tacrolimus. *Ther Drug Monit*. 2005;27(5):587-91.
- Zortress [package insert]. Stein, Switzerland: Novartis Pharma Stein AG; 2019.

104