



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Transplant Immunosuppression for the Boards

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DISCLOSURES

I have no relevant financial relationships with ineligible companies.



OBJECTIVES

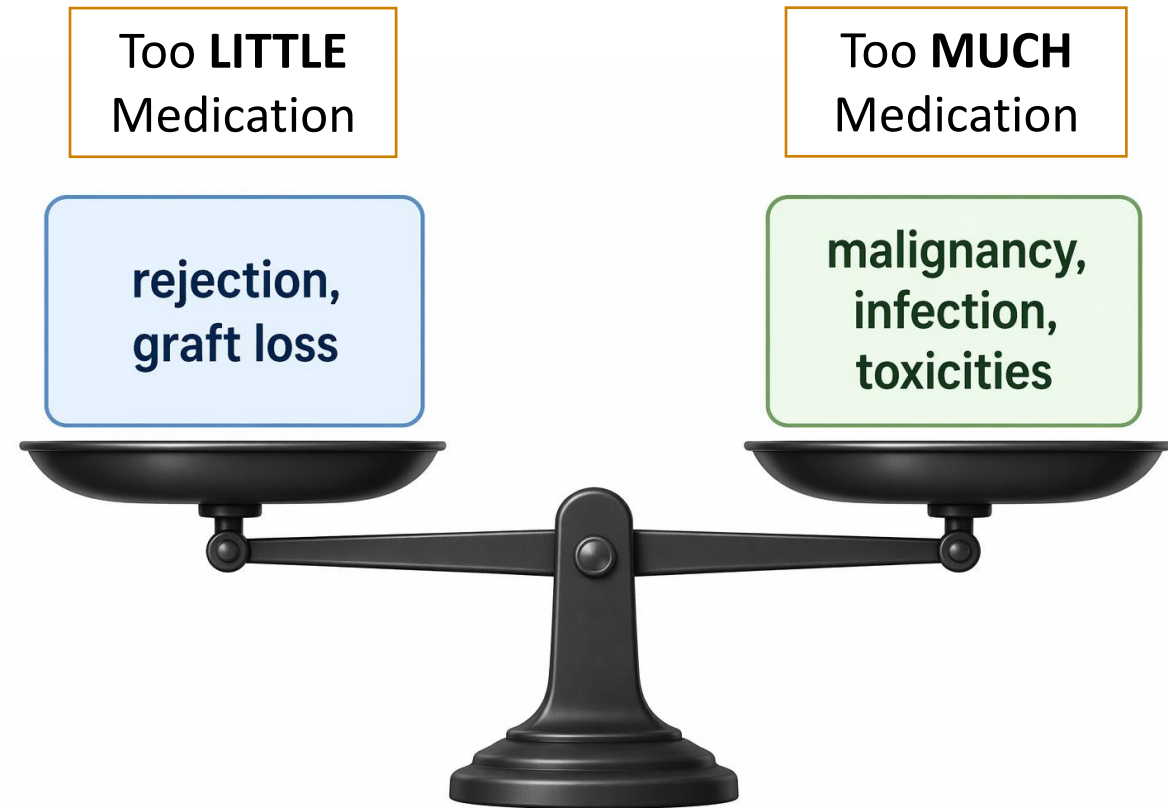
Describe the mechanisms of action, side effects, and toxicities of kidney transplant immunosuppression therapies

Review interactions that may occur with medications used in kidney transplant patients



Goals of Immunosuppression

- Balancing act with goal to improve patient and graft survival
- Combination therapy
 - Optimize immunosuppression using overlapping/synergistic mechanisms
 - Minimize side effects
- Individualized regimens



Kidney Transplant Immunosuppressive Regimens

Induction Therapy

Maintenance Therapy

Rejection Treatment





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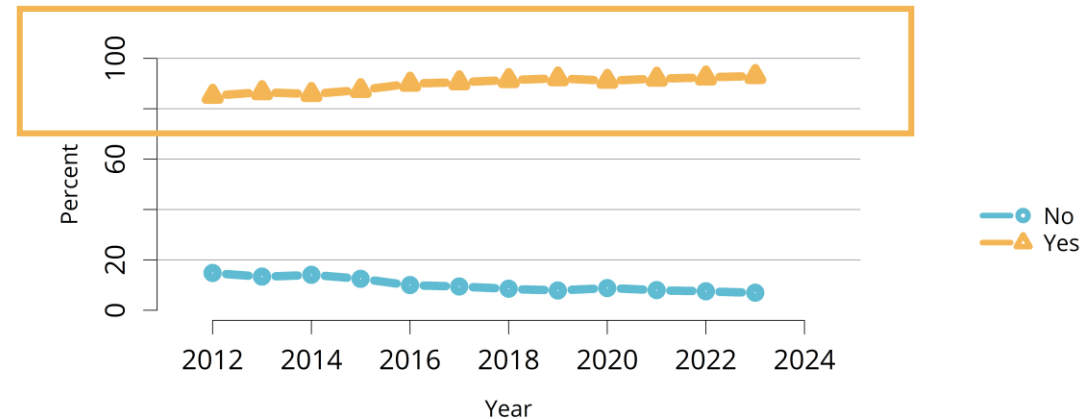
Induction Immunosuppression

Adult Kidney Transplant Induction Trends (OPTN/SRTR 2023 Annual Data Report)

Induction Therapy

- Intense therapy at time of transplantation
- Decrease rate of acute rejection
- Minimize/delay use of maintenance immunosuppression

Figure KI 45: Induction agent use in adult kidney transplant recipients



OPTN/SRTR 2023 Annual Data Report

Figure KI 45: Induction agent use in adult kidney transplant recipients. Immunosuppression at transplant reported to the OPTN.

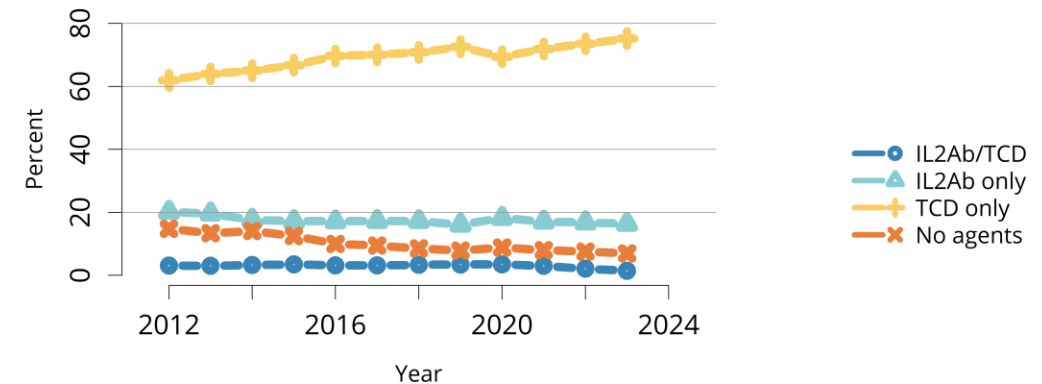


Adult Kidney Transplant Induction Trends (OPTN/SRTR 2023 Annual Data Report)

Induction Therapy

- **T-cell depleting (TCD):**
 - Rabbit antithymocyte globulin (Thymoglobulin)
 - Alemtuzumab (Campath)
- **Interleukin-2 receptor antibody (IL2Ab):**
 - Basiliximab (Simulect)

Figure KI 46: Type of induction agent use in adult kidney transplant recipients



OPTN/SRTR 2023 Annual Data Report

Figure KI 46: Type of induction agent use in adult kidney transplant recipients. Immunosuppression at transplant reported to the OPTN. IL2Ab, interleukin-2 receptor antibody; TCD, T-cell depleting.



Options for Induction Therapy

1. **Polyclonal** antibodies: react with multiple antigen receptors
 - Rabbit antithymocyte globulin (Thymoglobulin[®])
 - Equine antithymocyte globulin (ATGAM[®])
2. **Monoclonal** antibodies: react with a single antigen receptor on the lymphocyte
 - Basiliximab (Simulect[®]) CD25 or IL-2 R
 - Alemtuzumab (Campath[®]) CD52 (through Campath Distribution Program)
 - Withdrawn from the market:
 - Muromonab-CD3 (Orthoclone OKT3[®]) CD3
 - Daclizumab (Zenapax[®]) CD25 or IL-2 R



Rabbit antithymocyte globulin (Thymoglobulin®) “rATG”

- Anti-thymocyte globulins: polyclonal antibodies created by immunizing animals with human lymphocyte, to create antibodies against human T cells
- Directed against various T-cell markers: CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA Class I and HLA-DR subsets, and β 2 micro-globulin
- Multiple mechanisms of immune modulation:
 1. T-cell depletion (complement-dependent lysis, activation and apoptosis)
 2. Modulation leukocyte-endothelium interaction
 3. B-cell apoptosis
 4. Impairs dendritic cell function
 5. Induction of regulatory T and natural killer T cells
- Duration of Activity: cellular reconstitution can take months



Rabbit antithymocyte globulin (Thymoglobulin®) “rATG”

FDA Indication	▪ Prophylaxis and treatment of acute rejection for kidney transplant recipients
Place in Therapy	▪ Higher immunologic risk patients ▪ Allows delayed CNI initiation ▪ Steroid withdrawal
Dosing	▪ Typically up to 1.5mg/kg daily x 4-7 doses (start 1st dose before reperfusion) ▪ Dosing per local institutional protocols
Administration Considerations	▪ Caution in patients with known rabbit allergy ▪ Pre-meds: steroids, diphenhydramine, and acetaminophen
Adverse Reactions	▪ Leukopenia, thrombocytopenia (dose modifications necessary) ▪ Infusion-associated reactions ▪ Serum sickness ▪ Malignancy, infection



Basiliximab (Simulect®)

- Chimeric monoclonal antibody that competitively ***inhibits the activation*** of lymphocytes by IL-2
- Binds to alpha subunit of IL-2 receptor (CD25) & acts as receptor antagonist on activated T cells
 - CD25 present only on activated and non-resting T cells
 - Prevents IL-2 activation and further expansion of T cells
- Does **NOT** cause cell lysis
- Duration of activity: saturates IL-2 receptor up to 30-45 days



Basiliximab (Simulect®)

Place in Therapy

- Lower immunologic risk patients (e.g. 2 haplotype matched living donor)
- Significant infectious or malignancy history
- Lifetime burden of immunosuppression
- Known intolerance to rATG or alemtuzumab
- Advanced age

Dosing

- 20mg IV on Day 0 and Day 4

Administration Considerations

- Pre-medication **not necessary**



Case Question

KT is a 75 yo M (weight 67 kg) with a PMH significant for CKD stage 4. Has acquired solitary kidney due to renal cell carcinoma and is s/p right native nephrectomy from the year prior.

He is now scheduled for a pre-emptive living kidney transplant from his brother.

cPRA 0%. Negative B/T cell cross-matches. No DSA. 6/12 antigen mismatch.

Which induction should KT receive?

- A. Basiliximab 20 mg IV on POD 0 and 4
- B. rATG 1.5 mg/kg (100 mg) on POD 0, 1, 2, and 3
- C. Both A (basiliximab) and B (rATG) concurrently
- D. Immunosuppression induction is not indicated





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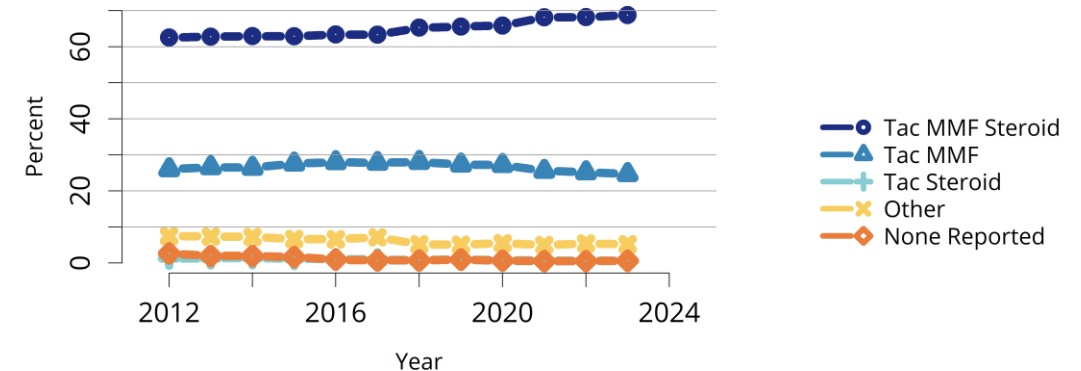
Maintenance Immunosuppression

Adult Kidney Transplant Maintenance Trends (OPTN/SRTR 2023 Annual Data Report)

Maintenance Therapy

- Less potent agents used for long-term immunosuppression post-transplant
- Prevent acute and chronic rejection
- Minimize drug-related toxicities
- Options Include:
 - **Calcineurin Inhibitors**
 - **Antimetabolites**
 - **Corticosteroids**
 - Co-stimulatory blockers
 - mTOR inhibitors

Figure KI 47: Immunosuppression regimen use in adult kidney transplant recipients

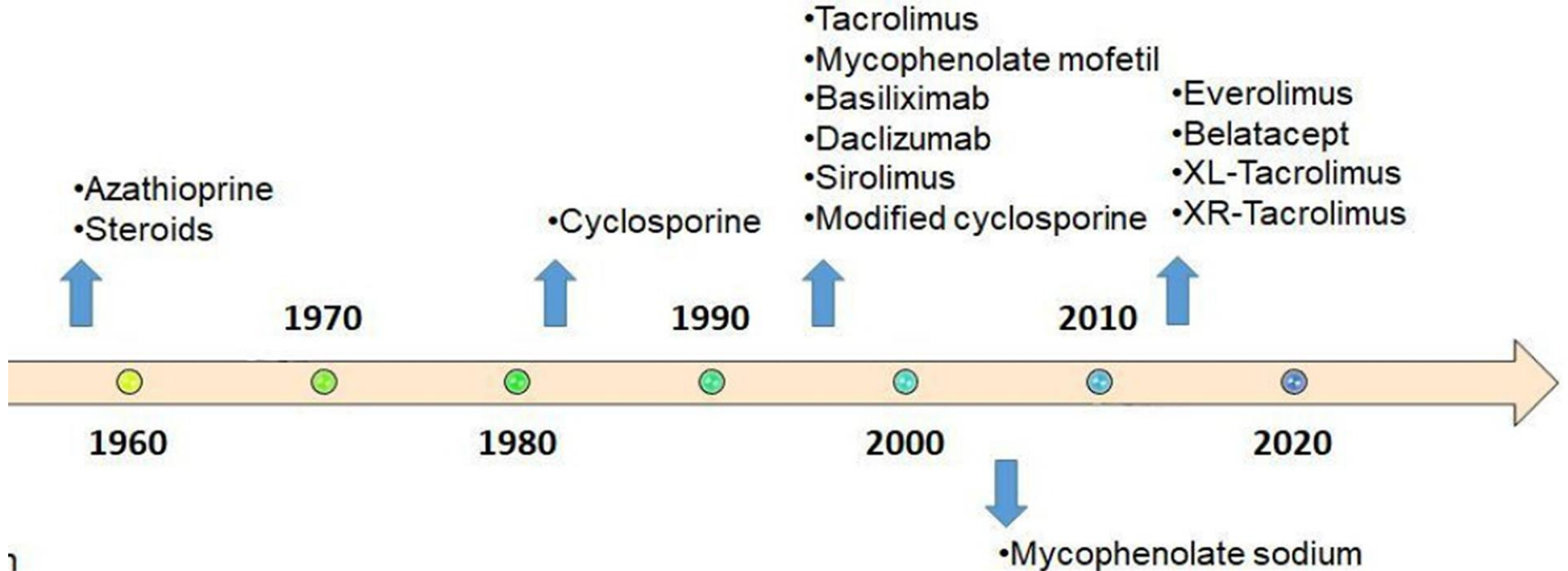


OPTN/SRTR 2023 Annual Data Report

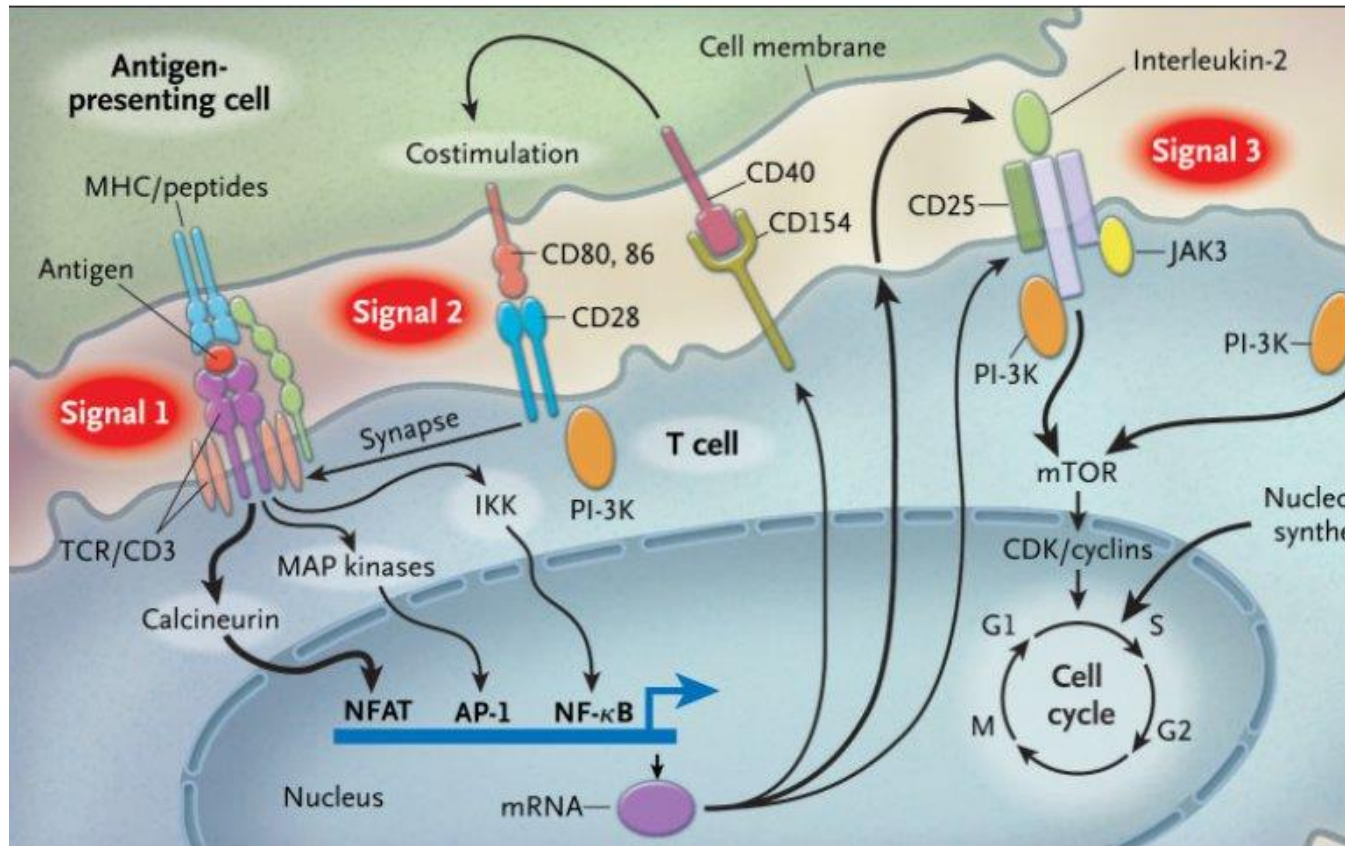
Figure KI 47: Immunosuppression regimen use in adult kidney transplant recipients. Immunosuppression regimen at transplant reported to the OPTN. MMF, all mycophenolate agents; Tac, tacrolimus.



Timeline of Maintenance Immunosuppression



The 3 Signal Model (Halloran, 2004)



Signal 1 –

CD3 complex: an Ag on the surface of dendritic cells triggers T cells with TCR.

Signal 2 (Co-stimulation) –

CD80 and CD86 on the surface of dendritic cells engage CD28 on T-cells.

Signal 3 –

“Target of rapamycin” pathway is activated by IL-2 and other cytokines. Results in cellular proliferation.

Halloran PF. N Engl J Med. 2004;351(26):2715-2729.

Basic Principles

Pharmacokinetics (PK): what body does to a drug (“ADME”)

Absorption

Distribution

Metabolism

Excretion

Pharmacodynamics (PD): what drug does to the body

Therapeutic Drug Monitoring (TDM)

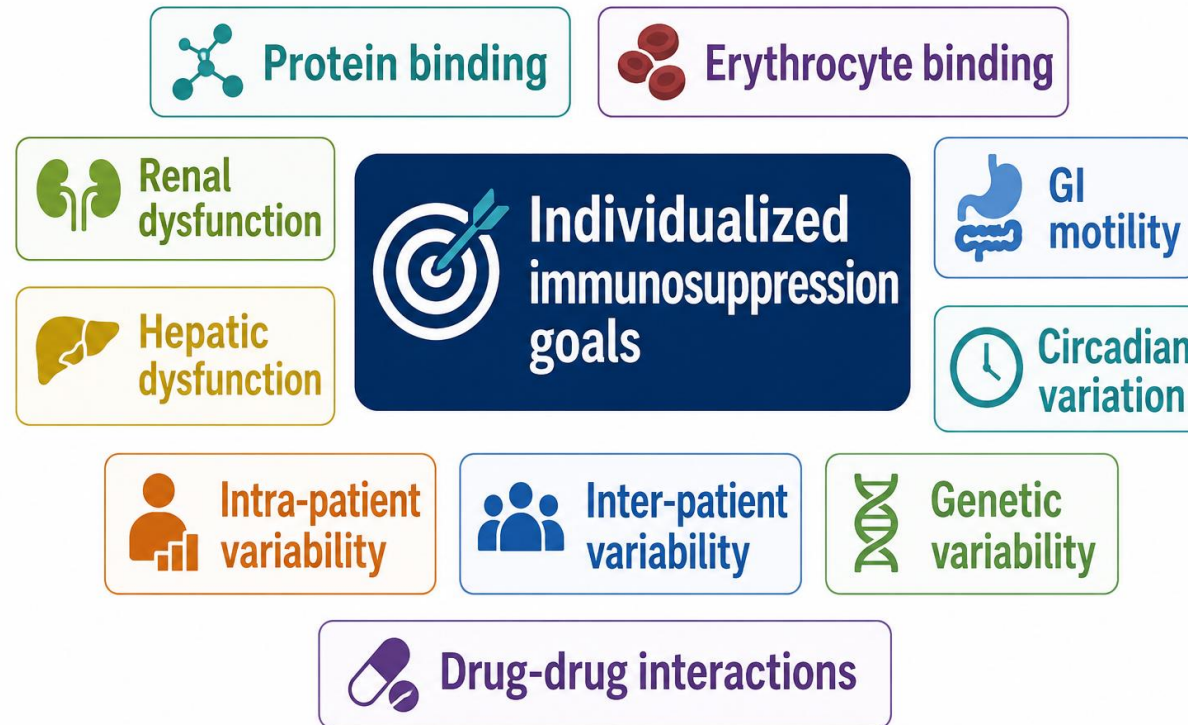


Examples of Drug Interactions

Pharmacokinetic interactions – Impact CNI/mTORi metabolism	
CYP 3A4 Inhibitors Decrease dose of substrate to account for <u>increase in exposure</u>	- Protease inhibitors (i.e. ritonavir, cobicistat) “-azole” antifungals - Macrolides (Erythromycin, Clarithromycin) - Diltiazem, Verapamil - Grapefruit
CYP 3A4 Inducers Increase dose of substrate to account for <u>decrease in exposure</u>	- Antiepileptics (phenytoin, carbamazepine, phenobarbital) - Rifamycin antibiotics - St. John’s Wort
Pharmacodynamic Interactions – Potentiate toxicity	
Additive nephrotoxicity	NSAIDs, Aminoglycosides
Additive marrow toxicity	Ganciclovir, Bactrim, Acyclovir
Immunomodulation	Echinacea, Vitamin C, Vitamin E



Influential Factors for TDM



ETC...

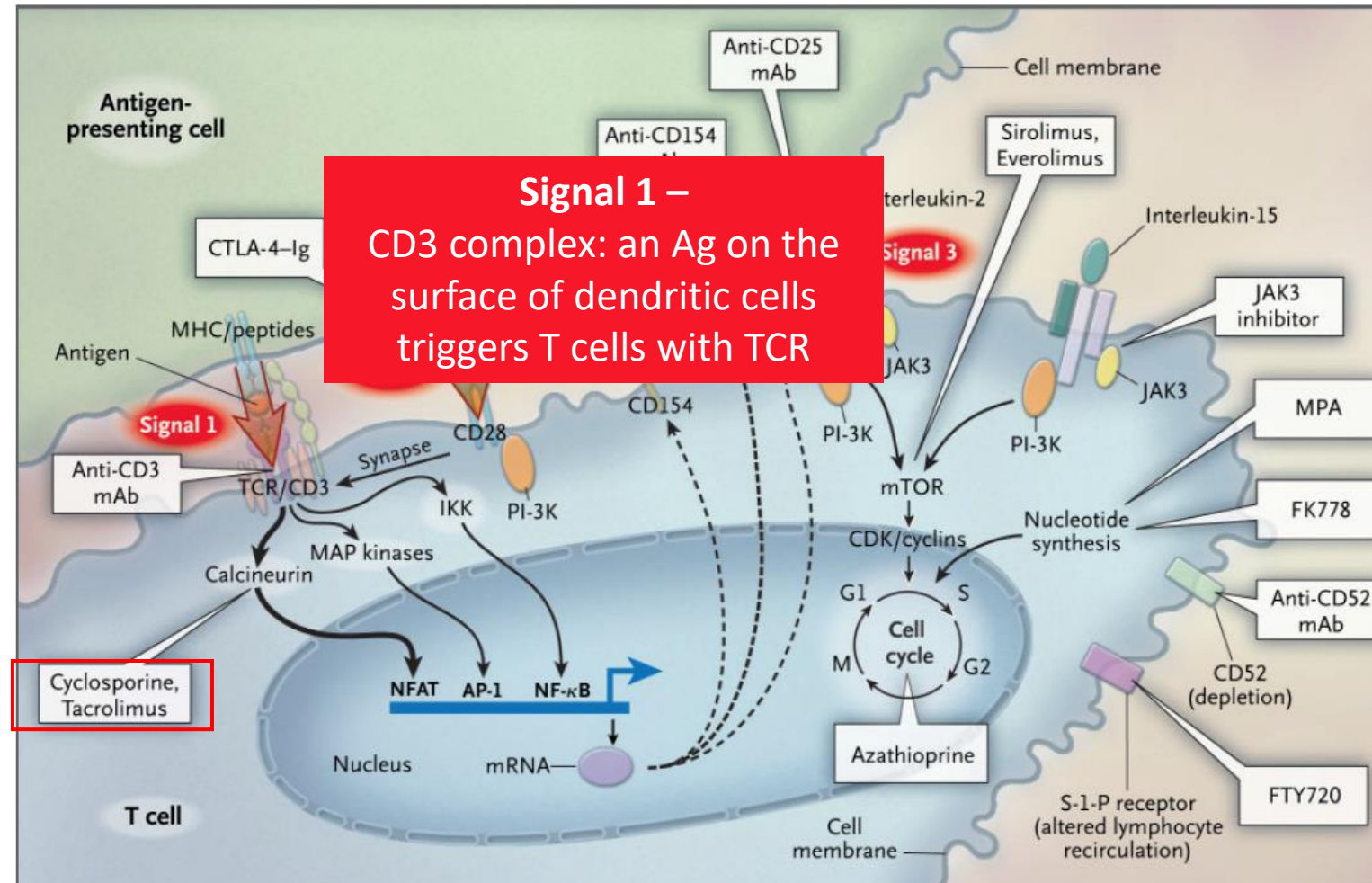
Calcineurin Inhibitors (CNIs)

Tacrolimus (Prograf[®], Astagraf XL[®], Envarsus XR[®])

Cyclosporine (Sandimmune[®], Neoral[®], Gengraf[®])



Calcineurin Inhibitors



Halloran PF. N Engl J Med. 2004;351(26):2715-2729.

Calcineurin Inhibitors – Efficacy

- Patient and allograft survival has been similar for the 2 CNIs
- **Acute rejection rates are reduced with TAC**

Recommendation (1A kidney, pancreas, liver; 1D intestine; 2B heart, lung). Tacrolimus is superior to CyA-ME for the prevention of allograft rejection. Additionally, it is superior for reducing the severity of rejection in kidney and pancreas transplants.

Recommendation (1A kidney, pancreas; 1B liver). Tacrolimus is associated with improved allograft survival compared to CyA-ME.

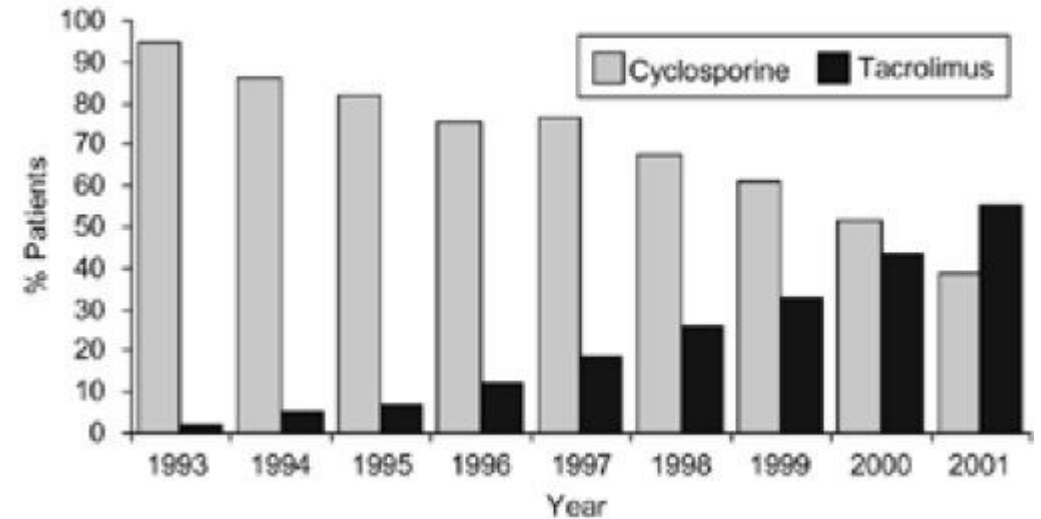


Figure 1 Kidney transplant immunosuppression prior to discharge: cyclosporine vs. tacrolimus, 1993–2001.
Source: 2002 OPTN/SRTR Annual Report, Table 5.6.

Calcineurin Inhibitors – Adverse Effects

	Tacrolimus	Cyclosporine
Neurotoxicity	↑↑↑	↑↑
Hyperkalemia	↑↑↑	↑↑
Hypophosphatemia/ Hypomagnesaemia	↑↑↑	↑
Alopecia	↑↑↑	n/a
Nephrotoxicity	↑↑↑	↑↑↑↑
Hypertension	↑↑	↑↑↑
Hyperlipidemia	↑↑	↑↑↑
Hirsutism	n/a	↑↑↑
Gingival hyperplasia	n/a	↑↑↑
Diabetes	↑↑	↑↑



Tacrolimus (Prograf)

“IR Tacrolimus”

Dosing

- Typically up to 0.1mg/kg/day (two divided doses every 12 hours)
- Titrated to institution-specific trough goal

Formulations

- Capsules (0.5mg, 1mg, and 5mg)
- Granules (tacrolimus for oral suspension)
- Oral suspension – only available through compounding pharmacies
- IV Solution

Administration Considerations

- PROGRAF® (tacrolimus) capsules or suspensions
 - Typically administered BID (12 hours apart)
 - Take consistently with or without food
- PROGRAF® (tacrolimus) injection, (for IV use)
 - Dose reduction from original PO dose required
 - Contains castor oil derivatives: risk of anaphylaxis
 - Increased harm and toxicity if converted/administered inappropriately
 - Variations between IV BID vs. continuous administration

Monitoring

- Trough (C_0) monitoring



ALL Tacrolimus Products (Prograf[®], Astagraf XL[®], Envarsus XR[®])

Absorption (Bioavailability)

- Oral: incomplete and variable
- Formulation dependent factors
 - Immediate vs. sustained release
 - **Astagraf XL (ER Tacrolimus):** Formulated with ethylcellulose to prolong drug release by controlling water permeation in the GI tract
 - **Envarsus XR (LCP Tacrolimus):** MeltDose technology to reduce drug particle size, resulting in ↓ surface area, ↑ solubility, & ↑ bioavailability
 - Enterally (PO cap, compounded suspension) vs. SL vs. IV
- Throughout GI tract
- **IR Tacrolimus:** Take consistently with or without food
 - Effect of administration with food (high fat): ↓ C_{max}
 - **ER or LCP:** package inserts state to take once daily on empty stomach



ALL Tacrolimus Products (Prograf[®], Astagraf XL[®], Envarsus XR[®])

Distribution

- High association with erythrocytes
- 99% plasma protein bound
- Affected by small intestine p-glycoprotein efflux pump

Metabolism

- Extensive via CYP 3A4 and 3A5 in liver and intestinal wall
- CYP3A5 polymorphisms influence tacrolimus metabolism
 - **Functional allele:** *1
 - **Non-functional allele:** *3, *6, *7
 - “Expressor” (CYP3A5*1/*1) require 2x dose to maintain similar exposure as “non-expressors” (e.g. CYP3A5*3/*3)

Elimination

- $t_{1/2}$ = varies per formulation
- Prolonged in hepatic dysfunction
- Primarily fecal elimination
- Minimal urinary elimination

	Average $t_{1/2}$ (hours)	Steady state (days)
Tacrolimus IR	12-18	2.5
Envarsus XR	31	7
Astagraf XL	38	7



Tacrolimus (Prograf) [package insert]. Northbrook, IL: Astellas Pharma US; 2012.
Envarsus XR [package insert]. Edison, NJ: Veloxis Pharmaceuticals, Inc.; 2023.

Astagraf XL [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2019.
Birdwell KA, et al. Clin Pharmacol Ther. 2015.
Niioka T, et al. Transplantation. 2012.

Tacrolimus (Prograf[®], Astagraf[®], Envarsus XR[®])

Linear, dose-proportional pharmacokinetics

Steady-state concentrations change in proportion to dose:

$$\frac{D_{\text{new}}}{C_{\text{SS,new}}} = \frac{D_{\text{old}}}{C_{\text{SS,old}}} \quad \longrightarrow \quad D_{\text{new}} = \frac{(C_{\text{SS,new}})}{(C_{\text{SS,old}})} \times (D_{\text{old}})$$

D – dose

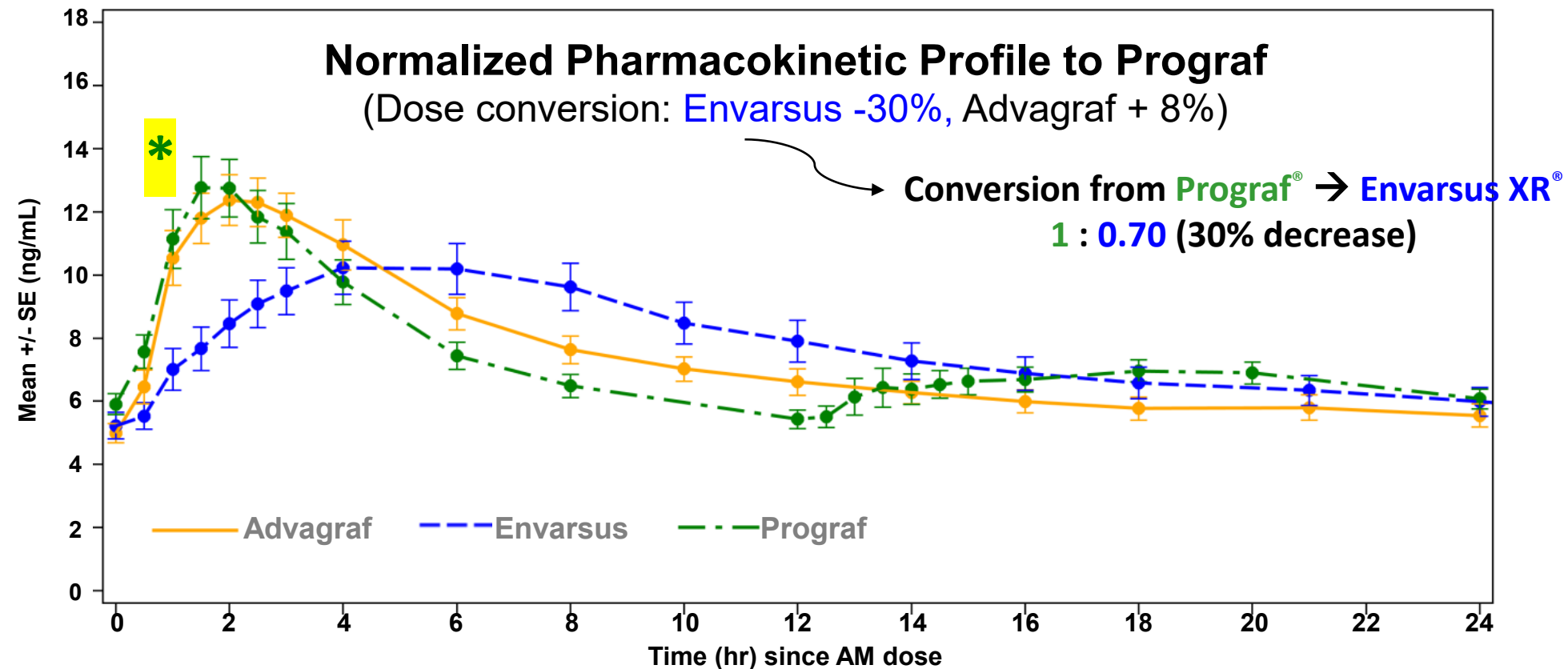
C_{ss} – steady-state concentration

old – the dose that produced the steady-state concentration that the patient is currently receiving

new – the dose necessary to produce the desired steady-state concentration



Comparison of Tacrolimus Formulations



* Tremors are a common adverse effect of tacrolimus, which can be most pronounced at peak serum concentrations



Case Question

KT is now POD #14 following kidney transplant.

His is on tacrolimus 5 mg PO BID and trough level is 9.2ng/mL (goal: 8-10 ng/mL).

However, KT shares that his hands are newly tremulous in the mornings. He reports that his friend also experienced the same thing after their kidney transplant, but improved after switching to Envarsus XR formulation. KT would also like to try that change.

What would be the most appropriate conversion dose of Envarsus for KT?

- A. Envarsus 5 mg PO qAM
- B. Envarsus 7 mg PO qAM
- C. Envarsus 10 mg PO qAM
- D. Envarsus 5 mg PO BID



ALL Cyclosporine Products

Cyclosporine (Sandimmune[®], Neoral[®], Gengraf[®])

Absorption

- Bioavailability:
 - Sandimmune[®]: poor & variable, dependent on bile
 - Neoral[®] or Gengraf[®] (modified): bioavailability is up to 30% higher
 - **These two formulations are NOT bioequivalent**
- Take consistently with or without food
 - Administration with food: ↓ in C_{max} and AUC

Distribution

- 90% protein bound – primarily bound to lipoproteins

Metabolism

- Extensive via CYP 3A4 system in liver and intestine

Elimination

- t_{1/2} = ~ 8 hours
- Approximate time to reach steady state = 2 days
- Biliary & highly variable



Cyclosporine: Sandimmune® vs. Modified Cyclosporine

These are NOT bioequivalent



Cyclosporine (Sandimmune®)

- non-modified, oil-based
- erratic and incomplete absorption
- dependent on presence of food, bile acids, and GI motility
- use has fallen out of favor

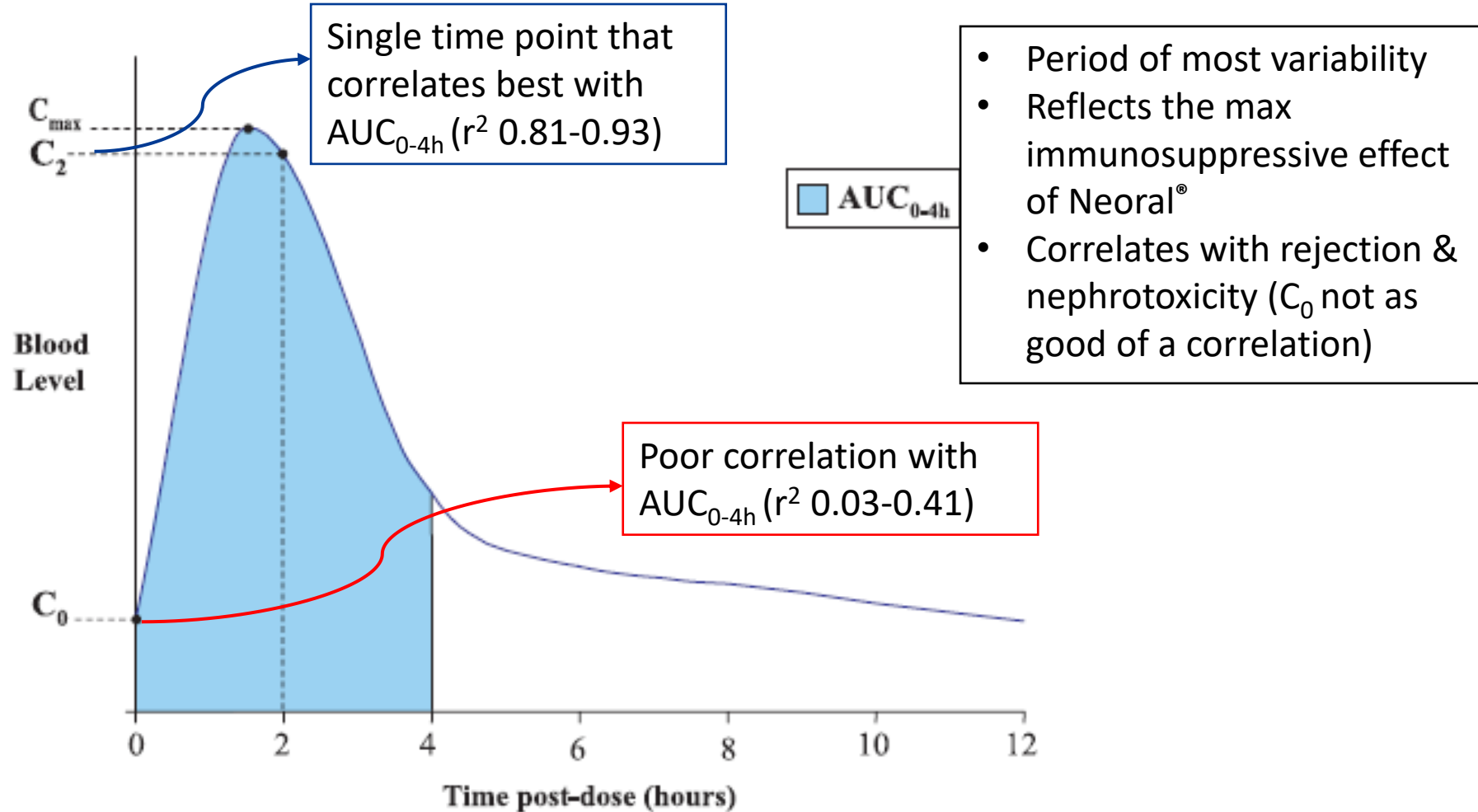


Modified Cyclosporine (e.g. Neoral®)

- microemulsion with improved bioavailability and consistent PK profile
- ↑'d absorption (up to 30%) when compared to Sandimmune®
- less dependent on food, bile acids, or GI motility



Cyclosporine Therapeutic Drug Monitoring (TDM)



Meier-Kriesche HU, et al. Transplantation. 2002;73(9 Suppl):S12-S18.

Kuypers DRJ, et al. Clin J Am Soc Nephrol. 2007;2(2):374-384.

Ekberg H, et al. Transplantation. 2007;83(12):1525-1535.

Alloway RR, et al. Am J Health Syst Pharm. 2012;69(22):1961-1975.

Cyclosporine: C_2 Monitoring

If C_2 is so great, then why are we using C_o (trough) for TDM?

Advantages

- Stronger correlation with AUC_{0-4h}
- Patients managed with C_2 's have lower rejection rates, require less cyclosporine and have better renal function

Disadvantages

- Practicality: small window (± 15 minutes)
- Potential for misinterpretation
- Studies demonstrating benefits are not well controlled and are single center reports



Calcineurin Inhibitor – Summarizing Use of TDM

- Refer to local institutional protocols for goals. General target troughs:
 - Tacrolimus: 5-15 ng/mL
 - Cyclosporine: 100-300 ng/mL
- Monitor frequently with medication initiation, dose adjustments, concomitant adjustment of interacting medications, etc.
- Increase frequency of monitoring when indicated:
 - interchanging medication formulations/manufacturers
 - suspected medication toxicity
 - rejection
 - other changes in patient condition: infection, diarrhea, liver injury
- Modify trough targets depending on individualized factors



Anti-Proliferatives

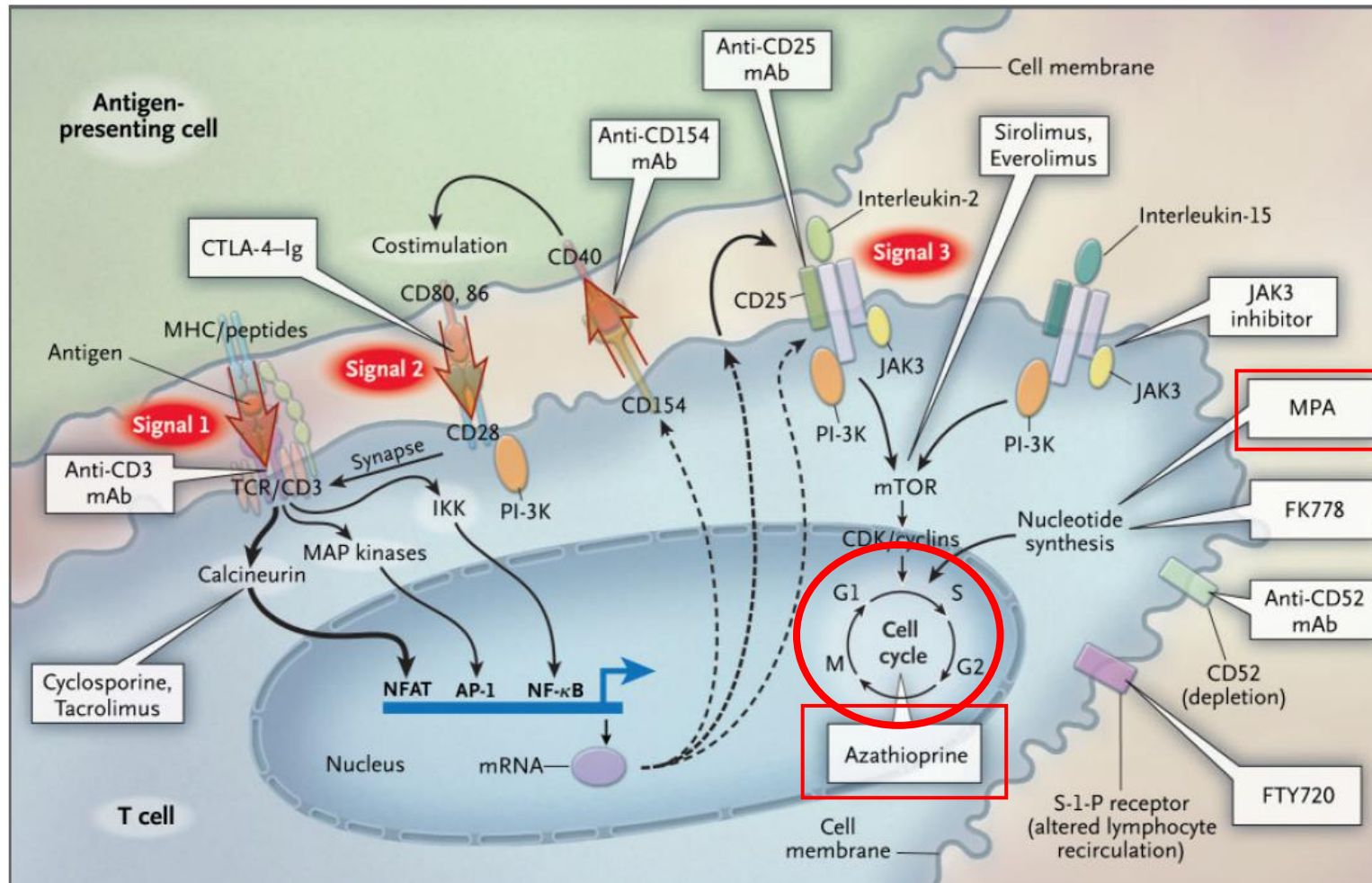
Azathioprine (Imuran[®], Azasan[®])

Mycophenolate mofetil (Cellcept[®])

Mycophenolate sodium (Myfortic[®])



Azathioprine and Mycophenolate (MPA)



Halloran PF. N Engl J Med. 2004;351(26):2715-2729.

MPA:

- Inhibits IMPDH resulting in inhibits purine synthesis
- Prevents T- and B- cell proliferation

Azathioprine:

- Prodrug of 6-MP (active) which is incorporated into DNA to inhibit purine synthesis and prevent formation of RNA
- Inhibits gene replication and T-cell activation



IMPDH: Inosine-5'-monophosphate dehydrogenase
6-MP: 6-mercaptopurine

Comparison of Mycophenolate Products

MYCOPHENOLATE MOFETIL (CellCept®)

- Mycophenolate mofetil (ester prodrug)
- **Active moiety: mycophenolic acid**
- Immediate release
- Absorbed in stomach (acidic medium)

MYCOPHENOLATE SODIUM (Myfortic®)

- Mycophenolate sodium (salt form)
- **Active moiety: mycophenolic acid**
- Delayed-release, enteric coated
- Absorbed in small intestines (neutral pH)

*These 2 formulations are **not bioequivalent***
mycophenolate mofetil 1000mg = mycophenolate sodium 720mg



	MYCOPHENOLATE MOFETIL (CellCept®)	MYCOPHENOLATE SODIUM (Myfortic®)
Absorption	Rapid absorption (30-60 min in stomach)	Delayed absorption (in small intestines)
	Take consistently with or without food Food decreases C _{max} but does not impact AUC	
Distribution	97% protein bound	
Metabolism	Metabolized by liver esterases to 2 main metabolites	
	• Mycophenolic Acid (active; “MPA”) • MPA glucuronide (inactive; “MPAG”) – “glucuronidation”	
	Enterohepatic Circulation (MPAG → MPA conversion): yields 2 nd peak, which accounts for 30% of circulating MPA	
Elimination	93% renal excretion t ½ = 18 hours	>60% renal excretion t ½ = 8-16 hours

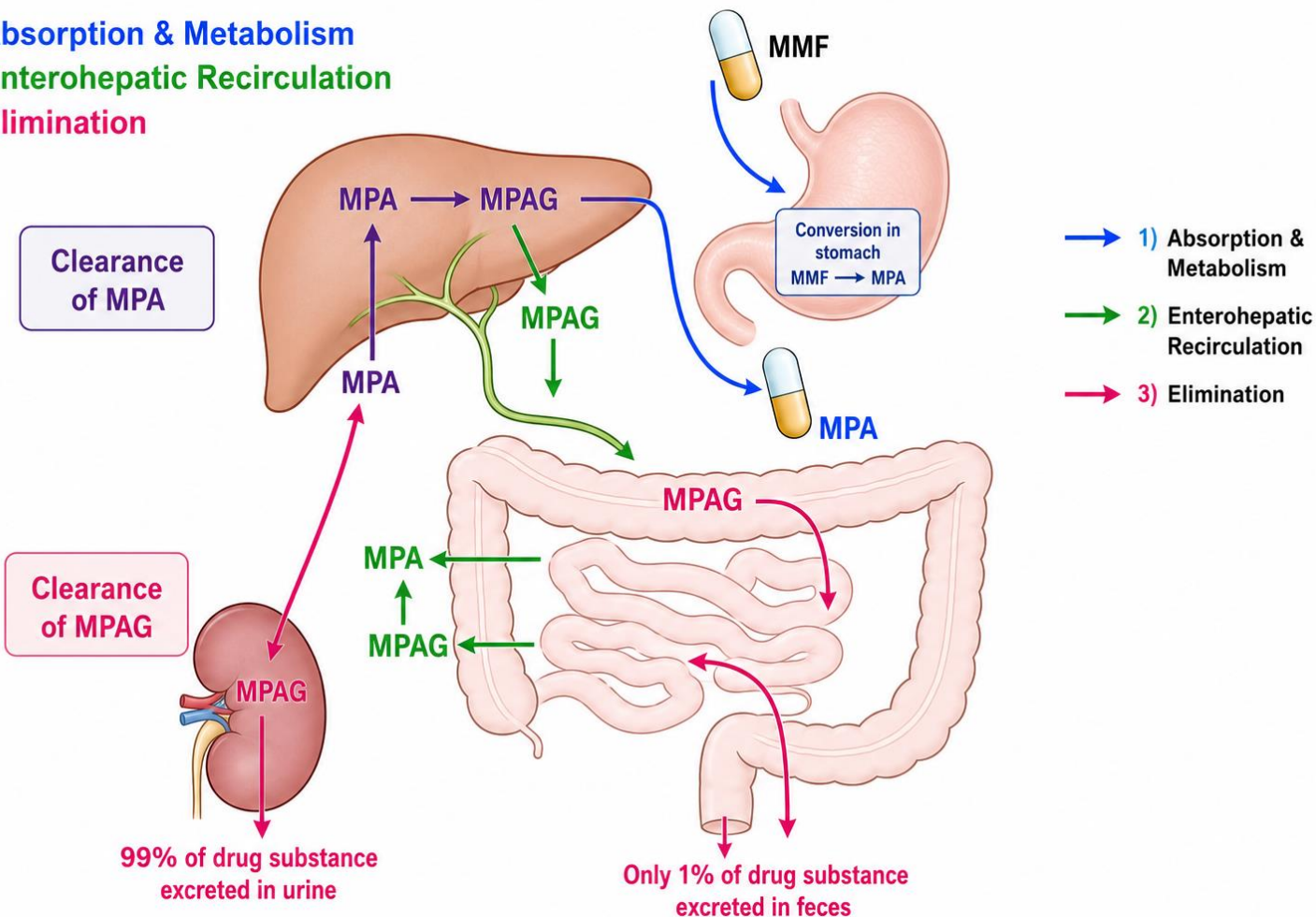


Mycophenolate Pharmacokinetic Profile

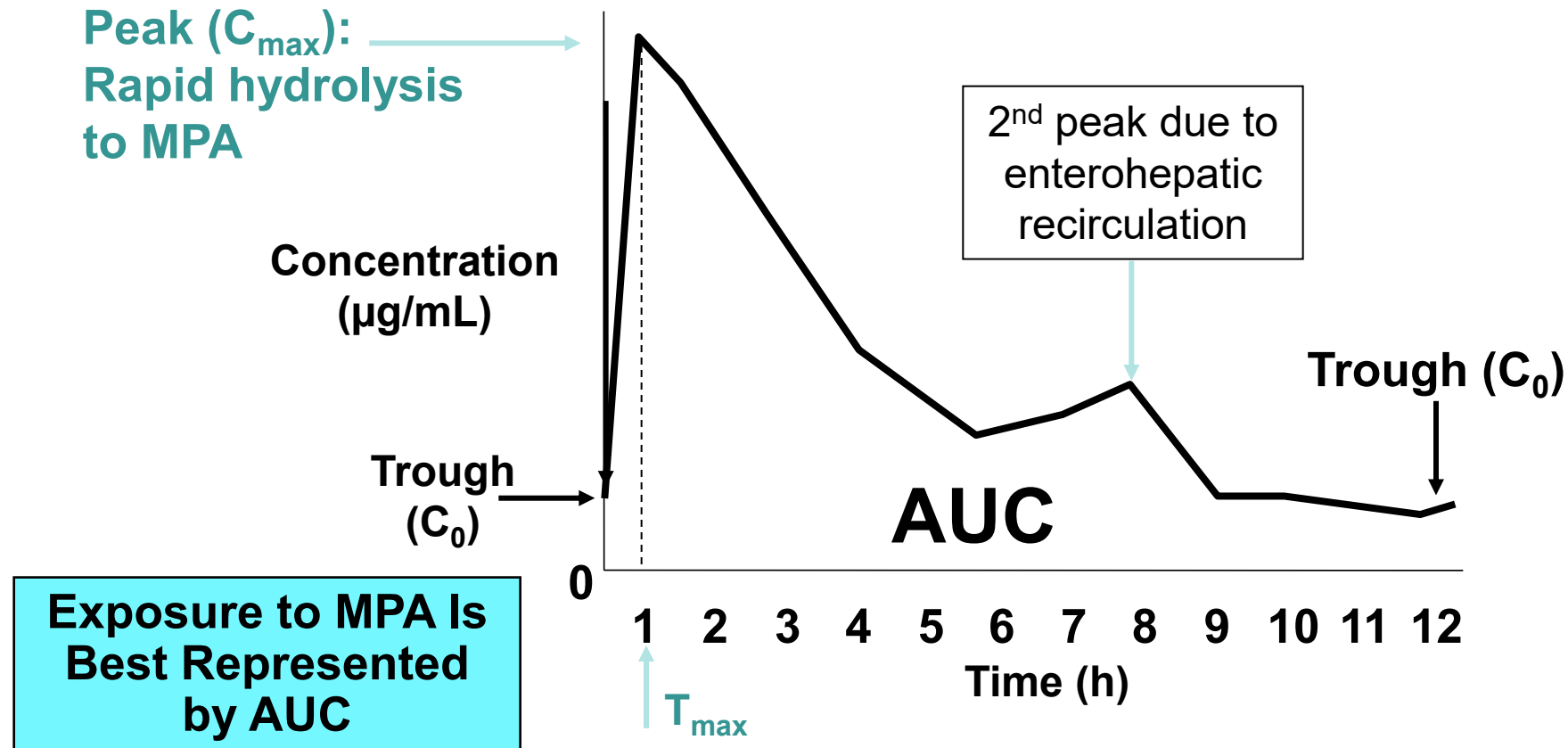
1) Absorption & Metabolism

2) Enterohepatic Recirculation

3) Elimination



How Is Exposure to MPA Best Represented?



AUC = area under the time-concentration curve; $C_{\max}$ = maximal or peak drug concentration; $T_{\max}$ = time to $C_{\max}$; C_0 = minimum or trough drug concentration



	Mycophenolate Mofetil (Cellcept[®], or “MMF”)	Mycophenolate Sodium (Myfortic[®])
Suggested Dosing for Adults	1000 mg twice daily	720 mg twice daily
Formulations	▪ Tablets (500mg) ▪ Capsules (250mg) ▪ Suspension (200mg/mL) ▪ IV solution (500mg vial)	▪ Enteric-coated tablets (180mg, 360mg)
Administration Considerations	Take consistently with or without food	
Monitoring	▪ Trough not correlated to AUC ▪ Routine TDM with MPA levels not recommended ▪ Mini-AUC may have role in setting of toxicity/malabsorption concerns	
Adverse Effects	▪ Gastrointestinal (nausea, vomiting, diarrhea) ▪ Hematologic (leukopenia, anemia)	
Select Drug Interactions	▪ Antacids; bile acid sequestrants; PPIs; sevelamer ▪ Cyclosporine – interferes with enterohepatic recirculation	



Mycophenolate Adverse Effects

- GI side effects are a major adverse effect of mycophenolate products: nausea, vomiting, diarrhea
- Strategies for GI side effect management:
 - Change mycophenolate mofetil (Cellcept) to mycophenolate sodium (Myfortic)
 - Fractionate mycophenolate from BID to QID dosing
 - Mycophenolate mofetil 1000 mg PO BID → 500 mg PO QID
 - Mycophenolate sodium 720 mg PO BID → 360 mg PO QID
 - Cautious reduction of mycophenolate dosage
 - Consider alternative antimetabolite (azathioprine)



Mycophenolate REMS

- Females of child-bearing potential must have Mycophenolate REMS Patient-Prescriber education reviewed: <https://www.mycophenolaterems.com>

ACCEPTABLE BIRTH CONTROL OPTIONS	
Talk with your doctor and pick from the following birth control options during treatment with mycophenolate.	
Option 1 Use Method Alone ■ Pick one item from (A) ▶ Most effective: Less than 1 pregnancy per 100 women in one year	A  Intrauterine Device (IUD)  Tubal Sterilization  Vasectomy
Option 2 Use Hormone & Barrier ■ Pick one item from (B) and one item from (C1) or (C2) shown below ▶ 4-7 pregnancies per 100 women in one year	B  Progesterone Only Injection  Birth Control Pill  Birth Control (Progesterone) Patch  Vaginal Ring  Progesterone Only Implant
Option 3 Use Two Barriers ■ Pick one item from (C1) and one from (C2) ▶ Least effective: 13 or more pregnancies per 100 women in one year	C 1  Female Condom  Male Condom 2  Female Diaphragm with Spermicide  Female Birth Control Sponge  Cervical Cap with Spermicide
To learn more about all the risks of taking mycophenolate, please see the Medication guide, which can be found at MycophenolateREMS.com	



Azathioprine (Imuran[®], Azasan[®])

Monitoring

- No standard monitoring required
- Consider checking TPMT activity, at baseline: complete (homozygous) or heterozygous TPMT deficiency predisposes patient to azathioprine adverse effects, compared to wild-type TPMT genotype

Adverse Effects

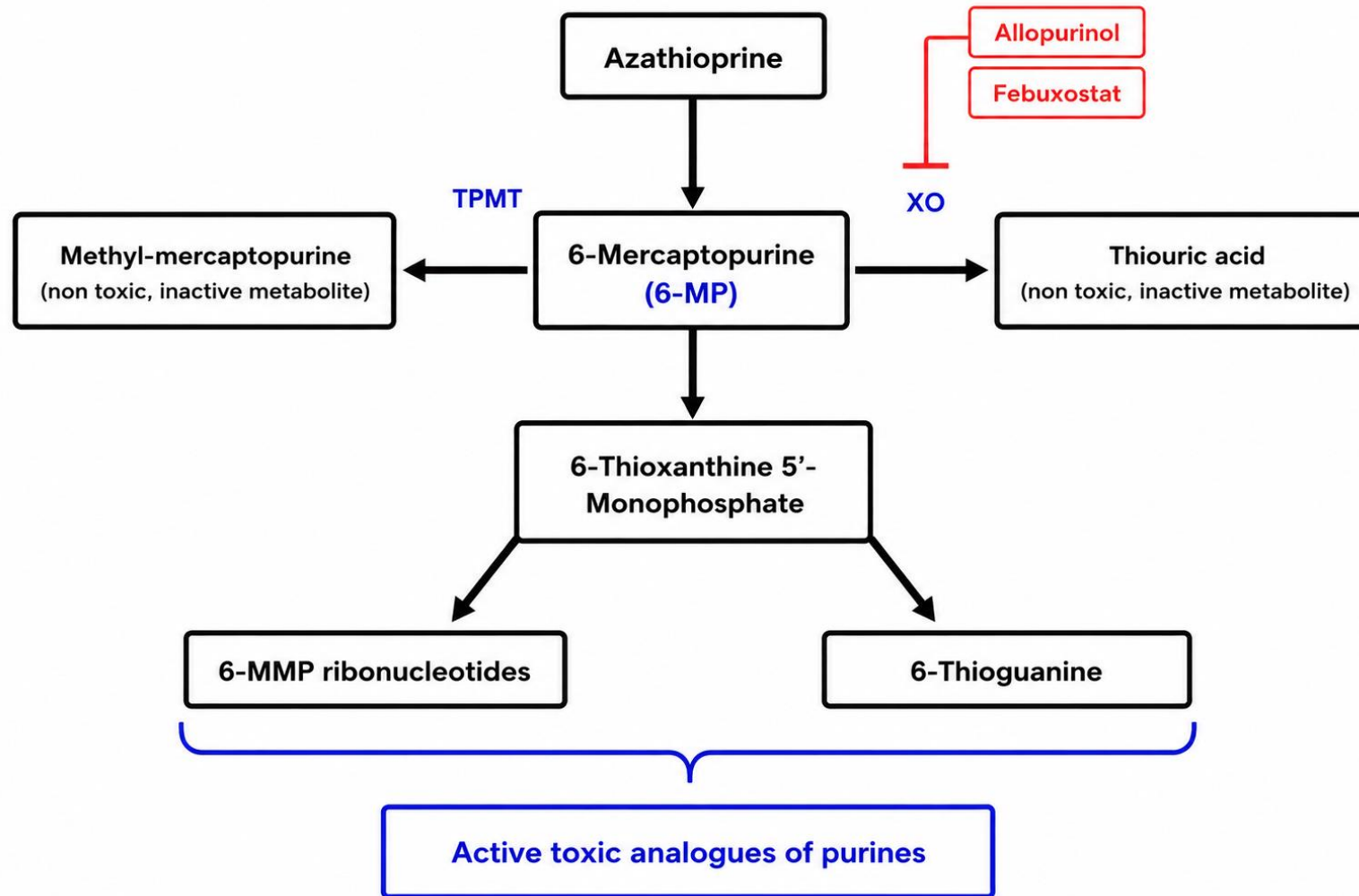
- Marrow suppression
 - Thrombocytopenia
 - Leukopenia
 - Anemia
- Fewer GI side effects compared with mycophenolate

Drug Interaction Potential

- Xanthine Oxidase Inhibitors (allopurinol & febuxostat)



Azathioprine (Imuran[®], Azasan[®])

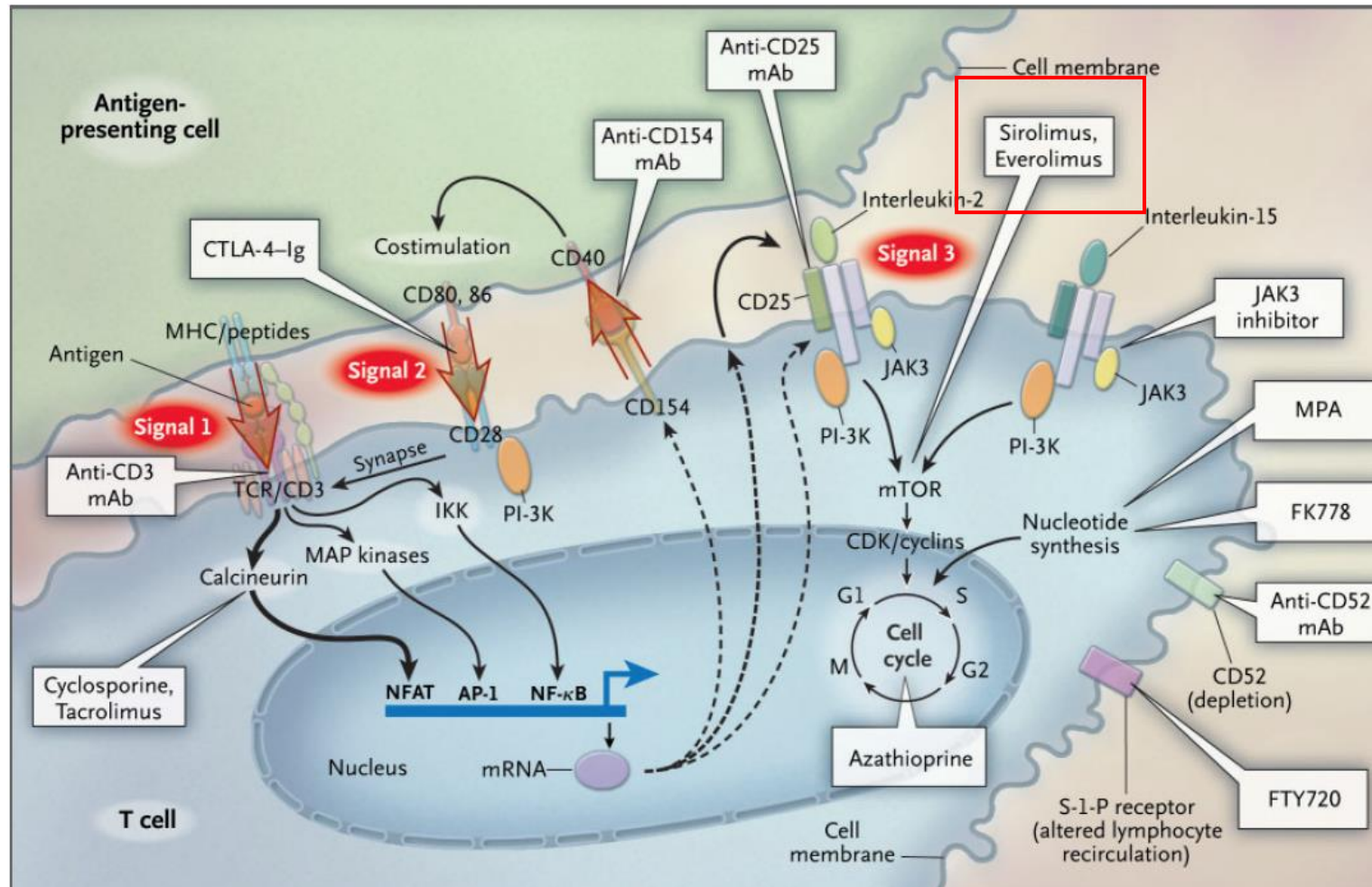


Mammalian Target of Rapamycin (mTOR) Inhibitors

Sirolimus (Rapamune®)
Everolimus (Zortress®)



Sirolimus and Everolimus



Halloran PF. N Engl J Med. 2004;351(26):2715-2729.

	SIROLIMUS (Rapamune®)	EVEROLIMUS (Zortress®)
Absorption	Peak concentrations within 1-2 hours Take consistently with or without food	
Food concerns	High fat meal $\uparrow$ AUC, $\uparrow$ $T_{\max}$, but $\downarrow$ $C_{\max}$	High fat meal $\downarrow$ $T_{\max}$, $\downarrow$ AUC, $\downarrow$ $C_{\max}$
Distribution	90% protein bound Substrate of P-gp	74% protein bound Substrate of P-gp
Metabolism	Extensive liver metabolism via CYP3A4	
Elimination	$t_{1/2} = 62 \pm 16$ hours Primarily in feces (inactive metabolites)	$t_{1/2} = 30 \pm 11$ hours Primarily in feces (inactive metabolites)
Monitoring	Trough (C_0) monitoring	



Impact of CNIs on mTOR Inhibitor Exposure

SIROLIMUS (Rapamune®)

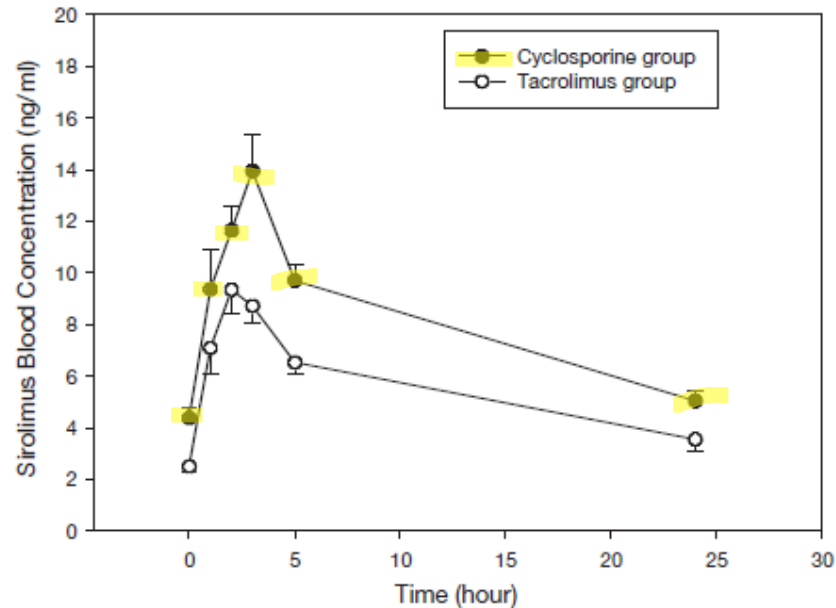
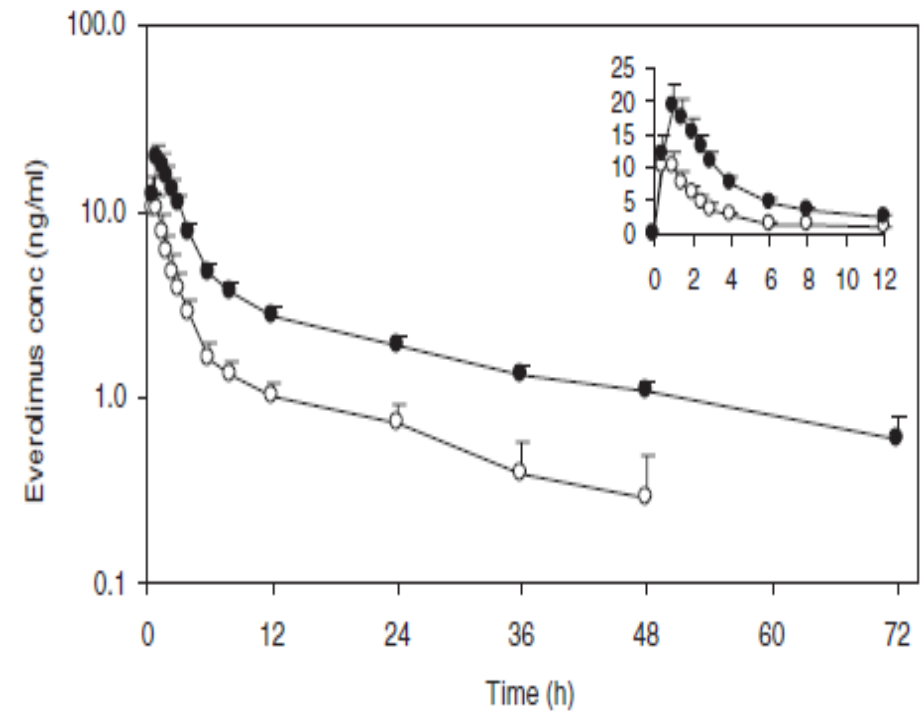


Figure 2. Sirolimus blood concentrations (mean $\pm$ standard error of the mean) in patients concomitantly treated with cyclosporine or tacrolimus.

EVEROLIMUS (Zortress®)



mTOR Inhibitors – Adverse Reactions

Impaired wound healing	Leukopenia/anemia
Rash/acne	Dyslipidemia
Pneumonitis	Proteinuria
Angioedema	Thrombosis



Corticosteroids

Methylprednisolone
Prednisone



Methylprednisolone and Prednisone

Mechanism for immunologic effects

- Higher doses (eg >100mg prednisone): induce T cell apoptosis
- Inhibition of IL-1, IL-2, IL-3, IL-6, IL-15, TNF- α and INF- γ
- Reduce T cell migration to inflammation

Cardiovascular effects

- Diabetes
 - Decrease insulin secretion and sensitivity
 - Increasing hepatic gluconeogenesis
 - Stimulating appetite and weight gain
- Hyperlipidemia
- Hypertension

Other effects

- Skeletal-muscle effects
- Ocular effects
- Behavioral/cognitive changes

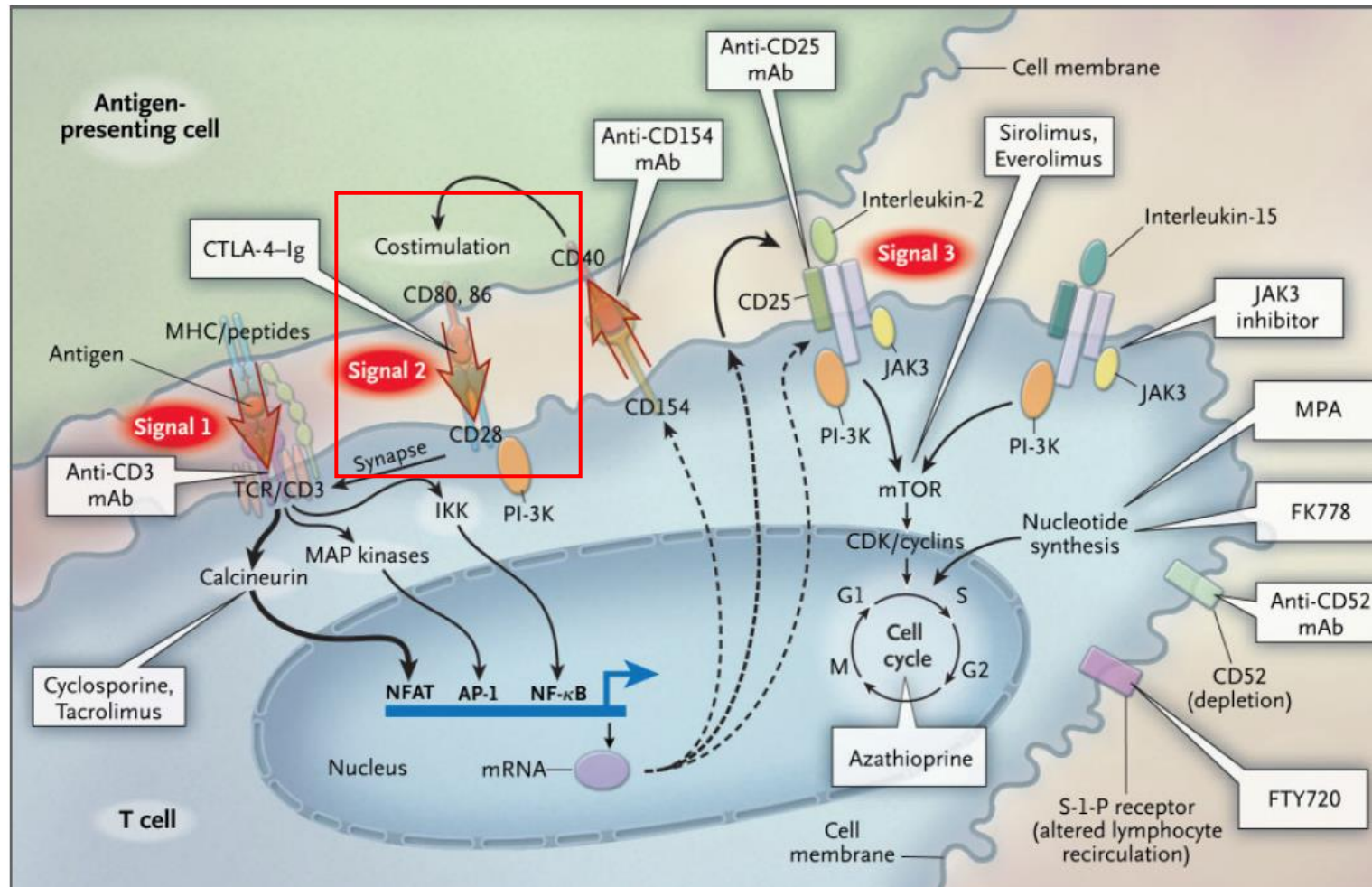


Co-stimulation Blockade

Belatacept (Nulojix®)



Belatacept (Nulojix®)



Halloran PF. N Engl J Med. 2004;351(26):2715-2729.

Belatacept (Nulojix®)

- Selective T-cell costimulation blocker (Signal 2)
- FDA-approved for prophylaxis of organ rejection in adult patients receiving a **kidney** transplant
- **Considerations:**
 - Only use in EBV seropositive patients (increased risk for developing post-transplant lymphoproliferative disorder "PTLD" for EBV naïve patients)
 - Transportation
 - IV access
 - Monthly maintenance infusion – infection, hospitalization, etc.

Dosing of NULOJIX for Kidney Transplant Recipients (2.1)

Dosing for Initial Phase	Dose
Day 1 (day of transplantation, prior to implantation) and Day 5 (approximately 96 hours after Day 1 dose)	10 mg per kg
End of Week 2 and Week 4 after transplantation	10 mg per kg
End of Week 8 and Week 12 after transplantation	10 mg per kg
Dosing for Maintenance Phase	Dose
End of Week 16 after transplantation and every 4 weeks (plus or minus 3 days) thereafter	5 mg per kg

- **Place in Therapy:**
 - Patients with CNI toxicity (neuro, renal, thrombotic microangiopathy)
 - Adherence concerns



Summary

- Immunosuppression safety and efficacy can be influenced by many variables. Medication monitoring requires a high level of attention to detail.
- Ongoing balancing act of risks and benefits of immunosuppression
- Consider patient-specific factors when establishing individualized goals
- Utilize therapeutic drug monitoring (TDM) when able



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