Alternative Immunosuppression Strategies in Solid Organ Transplant

Kristofer Gutierrez, PharmD, BCTXP Meredith H. Johnson, PharmD, BCTXP



Disclosure

The presenter(s) and presentation advisor(s) have no conflicts of interest or any relevant financial relationships to disclose.

Learning Objective

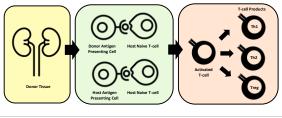
- Review the goals of post-transplant immunosuppression in preventing allorecognition
- Describe the current challenges of modern maintenance immunosuppression in solid organ transplantation
- Explain differences between immediate-release and extended-tacrolimus products
- · Identify alternative, renal-sparing immunosuppressive strategies
- Discuss the barriers and limitations of implementing novel maintenance immunosuppression regimens in solid organ transplantation

The Role of Post-Transplant Immunosuppression

 Prevention of allorecognition and subsequent allograft rejection or failure is the primary goal of any immunosuppressive regimen



Allorecognition of Donor Tissue

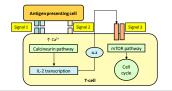


Halloran PF. New Engl J Med. 2004;351(26):2715-29

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The Three Signal Model of T-Cell Activation

 Interaction between donor antigenic material and recipient T-cells will promote secretion of interleukin-2 (IL-2) and T-cell proliferation



Moini M, et al. World J Hepatol. 2015;7(10):1355-69

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Immunosuppressive Regimens with Various Sites of Action

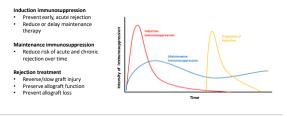
· Multi-drug combinations target different points in T-cell activation

- Individual agents with different mechanisms of action
 Minimization of dosages and drug-related toxicity
 Calcineurin inhibitors (CNI) are the backbone of most regimens

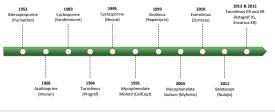


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Phases of Post-Transplant Immunosuppression

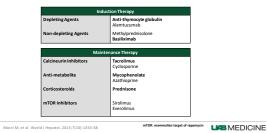


Timeline of Immunosuppressant Development

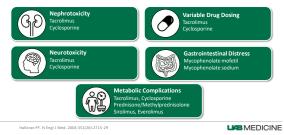


Wiseman AC. Clin J Am Soc Nephrol. 2016;11(2):332-43

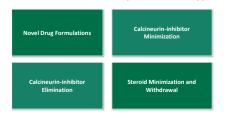
Common Immunosuppressive Agents



Current Challenges with Post-Transplant Immunosuppression



Alternatives to Standard Post-Transplant Immunosuppression



Limitations of Immediate-Release Tacrolimus

- Immediate-release tacrolimus (IR-tac) capsules associated with low bioavailability
 Tacrolimus simultaneously affected by P-glycoprotein (P-gp) and cytochrome P450 (CYP450) isoenzymes
 - · P-gp acts to transport drug molecules from the cell into the intestinal lumen
 - CYP450 isoenzymes metabolize tacrolimus into inactive metabolites

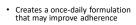


Prograf® (Tacrolimus). Astellas Pharm Inc.; Package Insert. Envarsus XR® (Tacrolimus extended-release). Veloxis Pharmaceuticals; Package Insert.

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Extended Release Calcineurin Inhibitor Formulations

- MeltDose[®] is a technology aimed at improving the solubility and bioavailability
- Reduces drug size down to single molecules in a solid suspension carrier matrix



Prograf® (Tacrolimus). Astellas Pharm Inc.; Package Insert. Envarsus XR® (Tacrolimus extended-release). Veloxis Pharmaceuticals; Package Insert.



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Efficacy and Safety Comparable Between Extended-Release and Immediate-Release Tacrolimus

· Prospective, double-blind, double-dummy randomized phase 3 trial

Patients	Interventions	Comparison	Outcomes
De novo kidney transplant recipients	Extended-release tacrolimus (LCPT) (n=268) plus matching placebo	Immediate-release tacrolimus (IR-tac) (n=275) plus matching placebo	Treatment failure at 2 years: 23.1 vs. 27.3% (non-inferior) Mean total daily dose at 2 years: 3.40.15 vs. 4.5±0.22 mg (p<0.001) Mean trough levels at 2 years: 5.47±0.17 vs. 5.8±0.30 ng/mL (p=NS)
		in-2 antagonist induction ith panel reactive antibout	with mycophenolate and corticosteroid dy >30%.

Rostaing L, et al. Am J Kidney Dis. 2016;67(4):648-59

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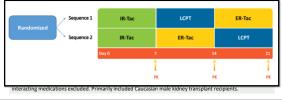
Extended-Release Tacrolimus Associated with Greater Drug Exposure

• ASTCOFF - Open-label, randomized, two-sequence, three period crossover trial

Patients	Interventions	Comparison	Outcomes
Stable renal transplant recipients*	IR-tac (baseline) >> LCPT for 7 days >> Extended-release tacrolimus capsules	IR-tac (baseline) >> ER-tac for 7 days >> LCPT for 7 days	Drug exposure as measured by 24-hour area under the curve (AUC) greatest with LCPT
*Tacrolimus and mycophenolate with or without prednisone	(ER-tac) for 7 days N=15	N=15	LCPT associated with delayed time to peak concentration LCPT associated with higher exposure per milligram of drug with less fluctuation
			n (within the previous 3 months), or e kidney transplant recipients.

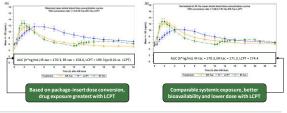
Extended-Release Tacrolimus Associated with Greater Drug Exposure

ASTCOFF – Open-label, randomized, two-sequence, three period crossover trial



Tremblay S, et al. Am J Transplant. 2017;17(2):432-42

Extended-Release Tacrolimus Associated with "Flatter" Pharmacokinetic Curve



Tremblay S, et al. Am J Transplant. 2017;17(2):432-42

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Pharmacokinetics of Extended-Release Tacrolimus Less Affected by Pharmacogenetic Differences

ASERTAA - Open-label, prospective, randomized, two-sequence, three period •

Patients	Interventions	Comparison	Outcomes
Stable, African- American renal transplant recipients*	IR-tac (baseline) for 7 days >> LCPT for 7 days	LCPT (85% of baseline dose) >> IR-tac for 7 days	LCPT associated with delayed time to peak concentration and lower peak level
*Tacrolimus and mycophenolate with or without prednisone	N=18	N=20	IR-tac: peak level 33% higher (p=0.04) CYP3A5 expressors vs. non-expressors on LCPT: peak level 11% higher
	ts with recent rejection specific antibodies exclu		onths), new interacting medications, BK
Trofe-Clark K, et al	. Am J Kidney Dis. 2017;71(3)::	315-26	

Clinical Utility of Extended-Release Tacrolimus Products

When should patients be considered for extended-release tacrolimus (Envarsus XR®)?

- Concern for adherence (once-daily vs. twice-daily administration)
- Excessive requirements with immediate-release tacrolimus .
- Rapid metabolizers of tacrolimus with CYP3A5 polymorphisms
- Intolerable neurotoxicity with immediate-release tacrolimus

Considerations for switching patients to extended-release tacrolimus (Envarsus XR®)?

- * Dosing conversion from IR-tac to LCPT (1 mg = 0.8 mg)
- Differences in drug absorption when switching to a more bioavailable drug formulation
- Insurance coverage and possible need for patient assistance program

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Post-Transplant Renal Dysfunction Negatively Impacts Patient Outcomes



Renal Dysfunctio

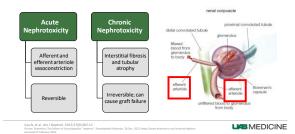
Contributing Factors to Post-Transplant Renal Dysfunction

Gonzalez-Vilchez F, et al. Drugs. 2014;74(13):1481-94

Calcineurin Inhibitors

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Calcineurin-Induced Nephrotoxicity



The mTOR Signaling Pathway: Promoter of Cell Growth and Motility

- . The mammalian target of rapamycin (mTOR) pathway involved with both physiological and pathological conditions
 - Promotes positive regulators of cellular activity (e.g., cytokines, vascular endothelial growth factor, insulin-like growth factor)
- Inhibition of mTOR pathway suppresses cytokine mediated lymphocyte proliferation Acts synergistically with calcineurin inhibition

Additional effects of mTOR inhibition include:

- Inhibition of oncogenic protein synthesis
 Inhibition of fibroblast and smooth muscle cell proliferation

Renal Benefit Greater with Calcineurin Elimination vs. Minimization

CNI-sparing vs. CNI-free regimen post-kidney transplant with sirolimus

Patients	Interventions	Comparison	Outcomes
De novo primary kidney transplant recipients	Sirolimus + low-dose tacrolimus + steroids (n=41)	Sirolimus + mycophenolate + steroids (n=29)	Estimated creatinine clearance at 1 year: 50.5 vs. 72.4 mL/min (p<0.05) Acute rejection at 1 year: 12 vs. 17% (p=NS)
Comments: Difference in renal benefit lost for donor age <50 years; less subclinical rejection with CNI-sparing regimen; more hematologic toxicity and wound complications with CNI-free regimen			

Lo A, et al. Transplantation. 2004;77(8):1228-35

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Calcineurin Inhibitor Elimination Improves Renal Function with High Risk for Rejection

Spare-the-Nephron – CNI vs. mTOR inhibitor (sirolimus) conversion post-liver transplant

Patients	Interventions	Comparison	Outcomes
Primary liver transplant recipients (4-12 weeks post-transplant)	Sirolimus + MMF + Steroids (n=148)	CNI + MMF + Steroids (n=145)	Change in creatinine clearance at 1 year: +14 vs3 mL/min (p<0.001) Biopsy-proven rejection: 12.2 vs 4.0% (p=0.02)
	cantly greater leukopen al secondary to adverse		al ulcers with sirolimus including more

Teperman L, et al. Liver Transpl. 2013;19(7):675-89

Calcineurin Inhibitor and mTOR Inhibitors with Potential Synergistic Nephrotoxicity

CNI-minimization with everolimus post-heart transplant

Patients	Interventions	Comparison	Outcomes
De novo heart transplant recipients	Everolimus + Low Cyclosporine + Steroids (n=282)	Full Cyclosporine + MMF + Steroids (n=145)	eGFR at 12-months: 59.4 vs. 64.7 mL/min/1.73m ² (p=0.009) Biopsy-proven rejection: 22.3 vs. 24.7% (p=NS)
		be related to protocol no cardial effusion, cytopeni	n-adherence; higher rates of drug ias, hyperlipidemia)

isen HJ, et al. Am J Transplant. 2013;13:1203-16

Clinical Utility of mTOR Inhibitors (Everolimus/Sirolimus)

When should patients be considered for mTOR inhibitor conversion?

- Calcineurin-inhibitor associated renal dysfunction
- Cardiac allograft vasculopathy post-heart transplantation
- Consider for liver transplant recipients with hepatocellular carcinoma Avoid if history of severe rejection, recent surgery, or severe renal impairment

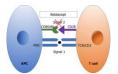
Considerations for switching patients to an mTOR inhibitor?

- Risk of post-transplant rejection or planned invasive surgical procedures
- Monitor for hyperlipidemia and/or proteinuria at baseline and periodically on therapy
- Serum drug level monitoring every 5 to 7 days given long half-life

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Co-Stimulation Blockade: A More Selective Immunosuppressive Therapy

- · Calcineurin inhibitors are a non-selective
 - Marcal and the second se Hypertension, diabetes, dyslipidemia



Belatacept is a selective co-stimulation blocker

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Efficient immunosuppression without the toxicities of calcineurin inhibitors

Kumar J, et al. World J Transplant. 2021;11(3):70-87

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Belatacept Maintains Long Term Improved Renal Function Post-**Kidney Transplant**

• BENEFIT - Outcomes with 7-year follow-up of belatacept vs. CNI

Patients	Interventions	Comparison	Outcomes
De novo primary	Belatacept:	Cyclosporine +	At month 84 (MI vs. LI vs. Cyclosporine)
kidney	More intensive regimen	MMF + Steroids	
transplant	(n=153)	(n=131)	Mean eGFR (mL/min/1.73m ²):
recipients			70.4 vs. 72.1 vs. 44.0 (p<0.001)
	Less intensive regimen		
(living or	(n=163)		Rates of acute rejection:
deceased donor)			24.4 vs. 18.3 vs. 11.4%
	MMF + Steroids		
			Risk of death or graft loss reduced by 43% with belatacept (p=0.02)
Commonte: All pat	tiontr received barilisimab	induction: ovcluded his	belatacept (p=0.02) h risk donors: excluded natients with nanel reactive

antibody ≥30-50%. Belatacept associated with significantly lower risk of donor specific antibodies.

Vincenti F, et al. N Engl J Med. 2016;374(4):333-43

Belatacept Dosing: More Intensive vs. Less Intensive Regimens



Transient Calcineurin Inhibitor Therapy Mitigates Rejection with Belatacept

· Retrospective review, belatacept vs. historical tacrolimus-based regimens

Patients	Interventions	Comparison	Outcomes	
De novo primary kidney transplant recipients (living or deceased donor)	Bela,/Bela, Bela/TaC _{pront} Off tacrolimus by 5 mo. Bela/TaC _{ccT(A)} Bela/TaC _{ccT(B)} Off tacrolimus by 11 mo. Basilikimab induction and MMF maintenance	Tacrolimus + MMF + Steroids (n=205)	eGFR 44 years significantly greater with belatacept (all regimend) vs. tacorolimus (all regimend) vs. tacorolimus Rejection rates at 3 & 12 months Tracrolimus 1718 v, 30.5% Bela/Tace _{sec} 158 vs. 50.5% Bela/Tace _{sec} 158 (12 months) No significant difference in patient or graft survival at three vears with belatacep vs. tacorolimus	
	Comments: Primarily African American patients in each group; more than one-third of patients with panel reactive antibody of 21-80% or >80%. Belatacept associated with significantly lower risk of donor specific antibodies.			

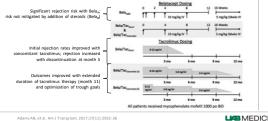
Adams AB, et al. Am J Transplant. 2017;17(11):2922-36

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Immunosuppressive Protocols Modified to Address Increased Rejection with CNI-free Regimens





Clinical Utility of Co-stimulation Blockers (Belatacept)

When should patients be considered for belatacept?

- · Low immunologic risk kidney transplant recipients without history of recent rejection
- At risk for calcineurin-inhibitor related renal or non-renal toxicity
- Concern for adherence with oral medications

Considerations for switching patients to belatacept?

- Patients must have a documented positive Epstein-Barr virus (EBV) serostatus
- Insurance coverage and possible need for patient assistance program
- Patient must have means of transportation and/or caregiver support to attend infusion clinic appointments

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Learning Assessment #1

AT is a 19-year-old African American kidney transplant recipient transitioning from pediatric to adult transplant care. He is moving away for college and has concerns about forgetting medication doses without his mom. He is a rapid metabolizer requiring tacrolimus 12 mg twice-daily. He has had two episodes of Banff 1B cellular rejection. He asks if there are immunosuppression options that would be easier for him to remember.

Which would be the best option for him?

- A. Belatacept-based regimen with concomitant tacrolimus B. Once-daily regimen of tacrolimus-extended release (Envarsus XR®)
- C. Once-daily sirolimus with calcineurin elimination D. Twice-daily everolimus with calcineurin-minimization

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Learning Assessment #2

YW is a 66-year-old Caucasian kidney transplant recipient (12 months ago) currently receiving tacrolimus 8 mg twice-daily with mycophenolate and prednisone. Recent lab work shows a slow decline in renal function over the last several months. He has no history of rejection post-transplant and has never missed any appointments or medication refills. Of note, he is EBV seronegative. YW asks about trying a new medication he saw online called belatacept.

Is YW a suitable candidate for a belatacept-based regimen?

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