



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

Transplant Immunosuppression for the Boards

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- Clinical focus: Transplant Nephrology, Onco-Nephrology
- Research focus: Regulatory T cell-derived extracellular vesicles; Autologous regulatory cell therapies

DISCLOSURES

I have no relevant financial relationships to disclose.

My presentation does include discussion of off-label or investigational use including alemtuzumab for induction therapy, all agents in corticosteroid free regimens, belatacept transition and everolimus transition/use with tacrolimus.



OBJECTIVES

- Outline the goals and principles of immunosuppression in kidney transplant recipients
- Classify and describe the mechanism of action of different immunosuppressive agents used in kidney transplantation
- Identify the different uses of transplantation immunosuppression and the relative benefits and drawbacks of different immunosuppressive agents



OUTLINE

- I. T cell Activation
- II. Induction Regimens
 - I. Overview
 - II. Available Agents
 - III. Clinical Data
- III. Maintenance Regimens
 - I. Available Agents and Mechanisms of Action
 - II. Calcineurin inhibitors (CsA v Tac)
 - III. Anti-proliferative (MPA v AZA)
 - IV. Steroids
 - I. Early and Late Withdrawal
 - V. CNI Avoidance
 - I. mTOR inhibitors
 - II. Co-stimulation Blockade

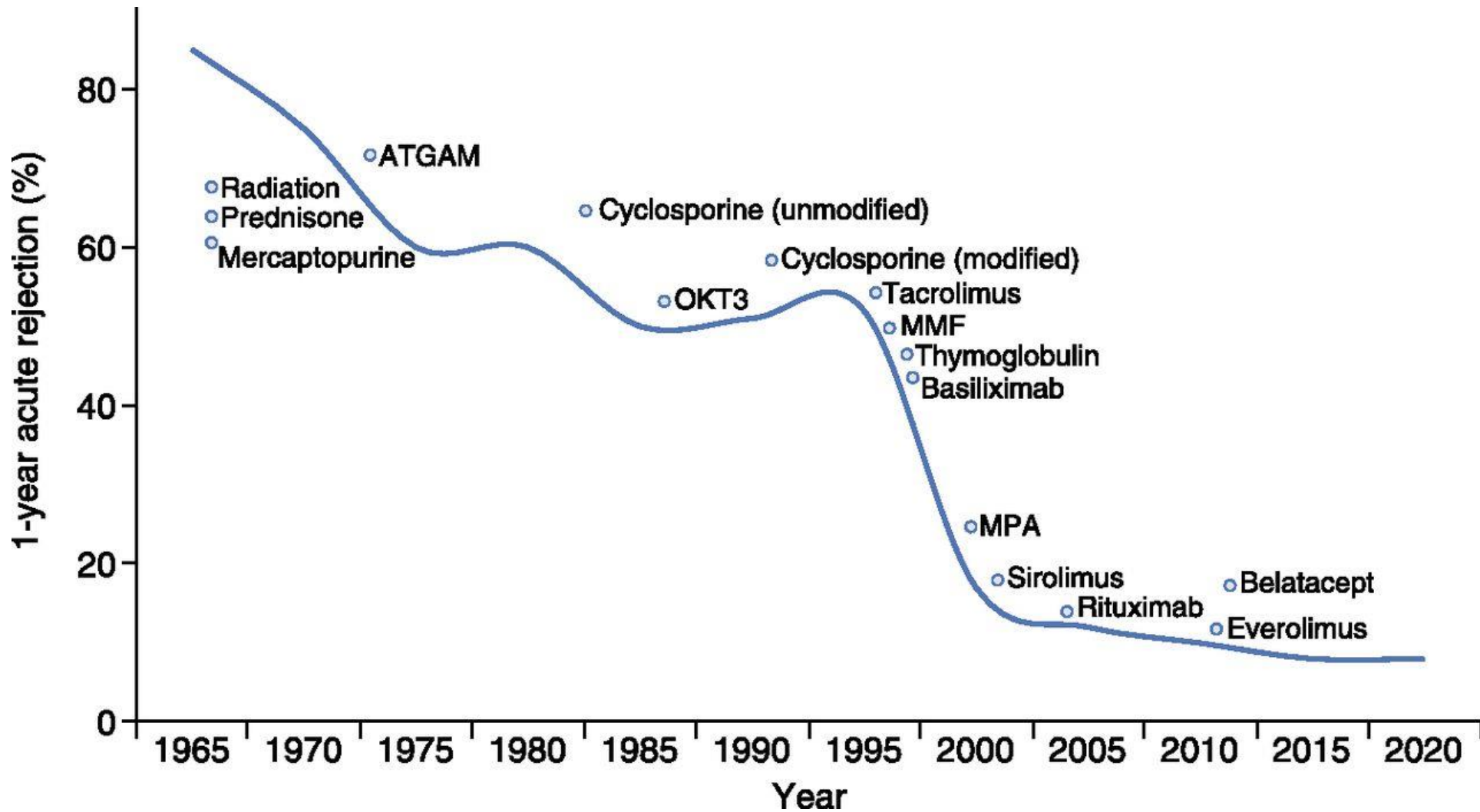


Goals of Immunosuppression

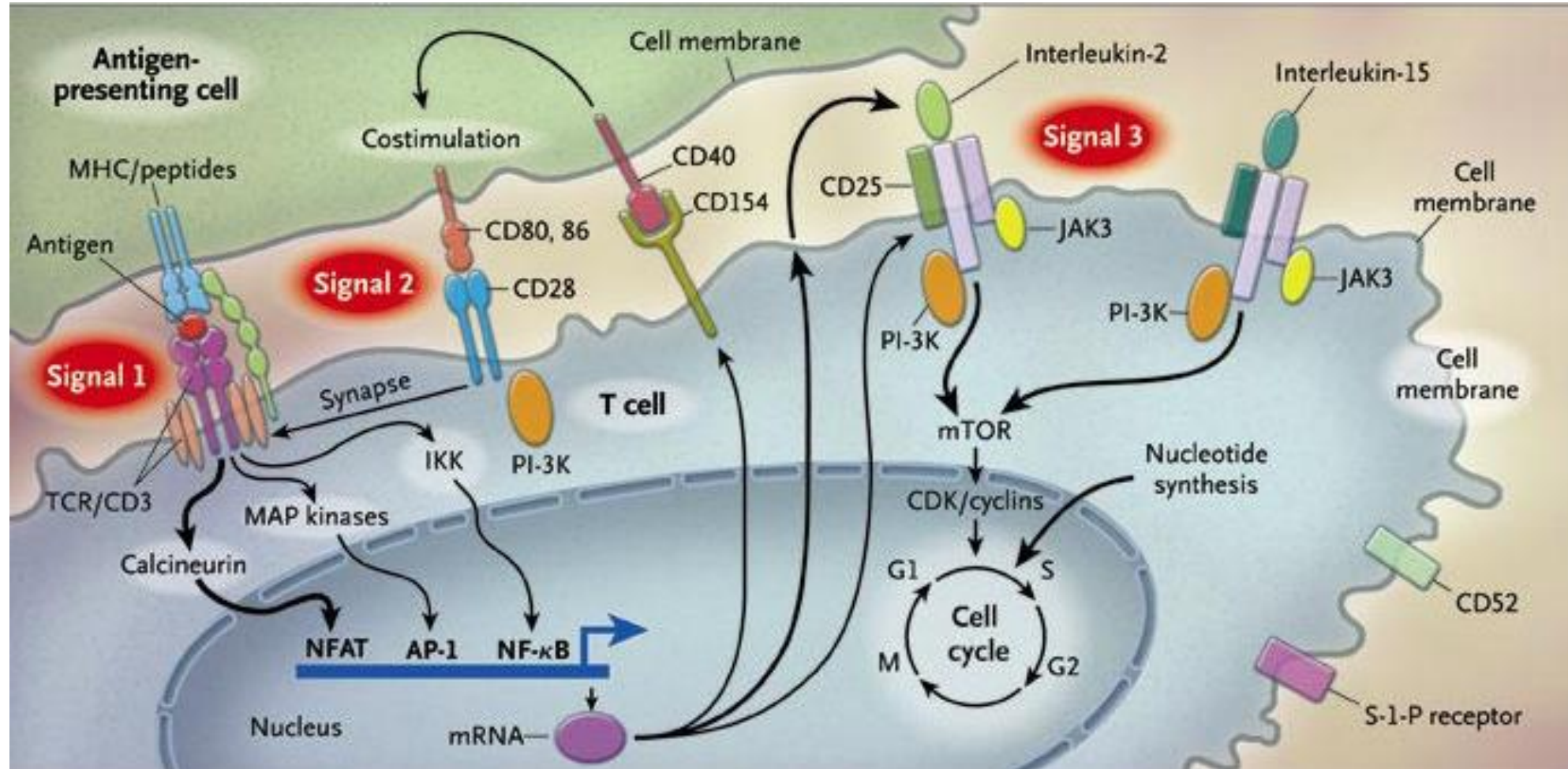
1. Suppress an alloimmune response to the donor kidney
 - Low rates of rejection
 - Decrease formation of donor specific antibodies
2. Minimize risk of infections and malignancy
3. Consider recipient's comorbidities (CVD, DM, etc)
4. Avoid nephrotoxicity



Timeline of Drug Development



Steps in T cell Activation



Poll Question:

- **Age/Sex/Race:** 33 y/o male
- **Cause of renal failure:** IgA nephropathy - focal proliferative type- current Cr 5.88/eGFR 11 more symptomatic with recent wt loss 15 lbs and fatigue
- **Dialysis status:** Pre-emptive
- **Potential donors:** Mom cleared for donation
- **Prior Transplant:** no
- **PMH:** non-contributory
- **Immunologic risk:**
 - Prior transfusion/pregnancy/transplant: no
 - Previous immunosuppression: no
 - Prior cancer: no
 - Prior severe infections: no
- **EBV pos; CMV neg; HCV neg ;HBV neg ;HIV neg**
- **PRA class I: Neg; PRA class II: Neg**
- **Planned Maintenance Immunosuppression:** TAC, MPA, early steroid withdrawal

What would you give for Induction Therapy:

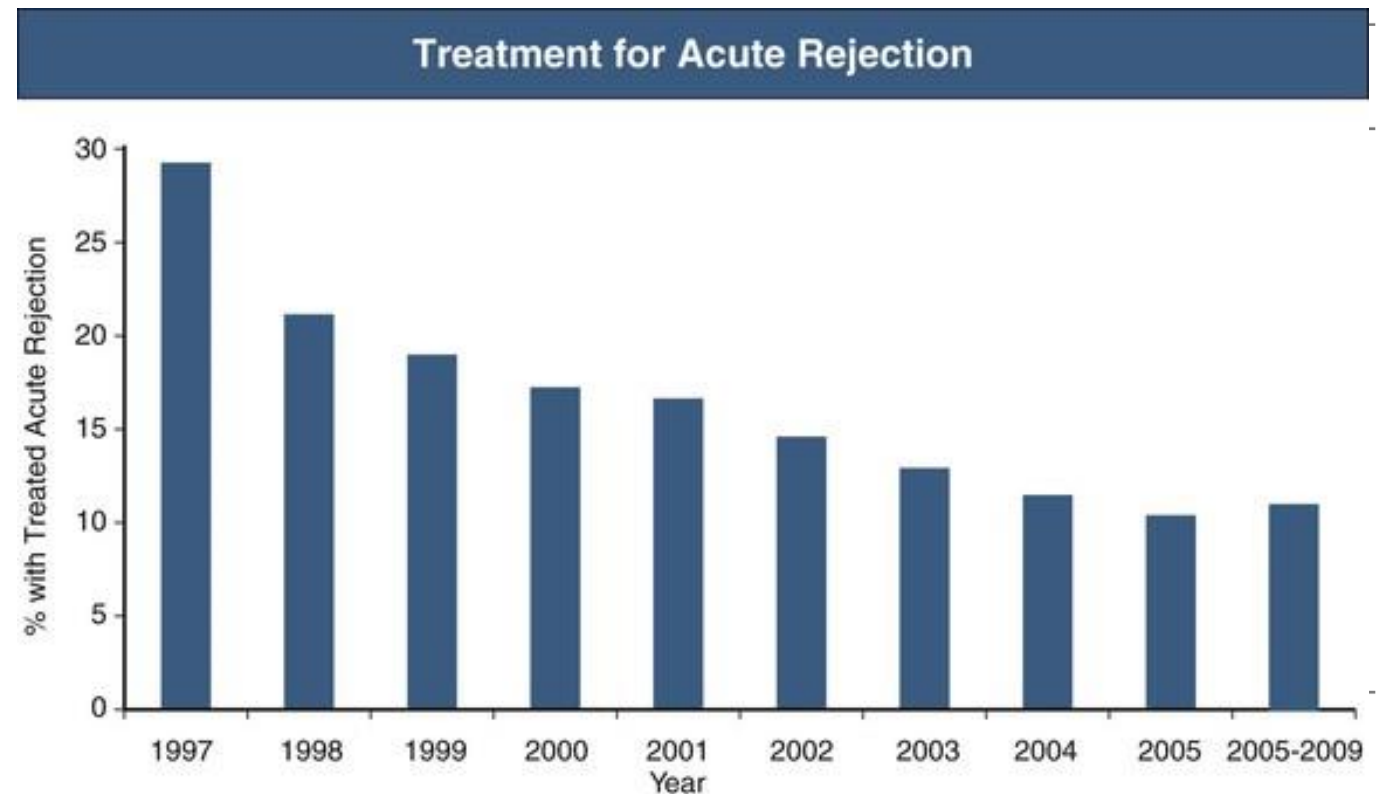
1. Alemtuzumab
2. Basiliximab
3. Rabbit anti-thymocyte Globulin
4. No induction therapy



Induction therapy is commonplace in kidney transplantation

- Induction used in 91.3% of renal transplants in 2021.
- Decreased rates of acute rejection.
- 2021: Acute rejection at 1 year:
 - Combination IL-2RA and Antilymphocyte antibody = 10.6%
 - IL-2 RA = 7.3%
 - Antilymphocyte antibody = 6.4%
 - No induction = 6.2%

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



SRTR Data from 2007 and 2012 reports



Induction Immunosuppression

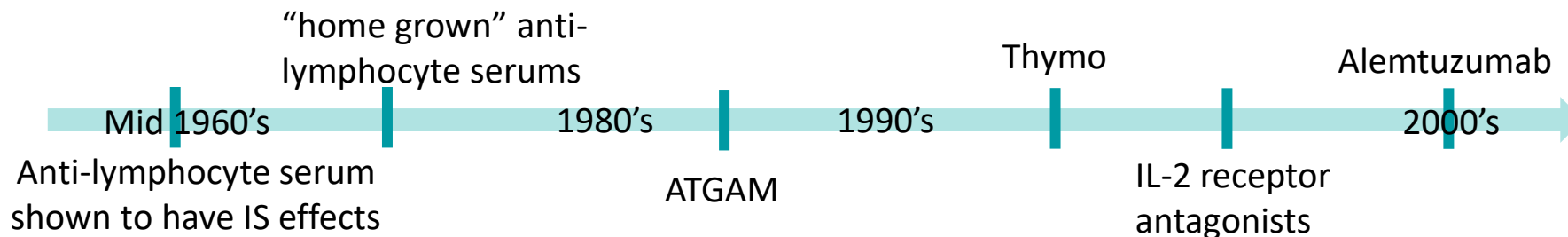
Goals of induction therapy

1. To decrease the rate of acute rejection
2. To permit delayed initiation, minimization or avoidance of some of the maintenance agents (i.e. CNI, corticosteroids)
3. To induce T-cell non-responsiveness

Available agents – Depleting v non-depleting

1. Monoclonal antibodies that react with a single antigen receptor on the lymphocyte
 - Basiliximab (Simulect®) – non-depleting
 - Alemtuzumab (Campath®) – depleting
 - Withdrawn from the market: muromonab-CD3 (OKT3) and daclizumab (Zenapax®)
2. Polyclonal antibodies: react with multiple antigen receptors
 - Equine polyclonal IgG antibody (ATGAM®) – depleting
 - Rabbit polyclonal IgG antibody (Thymoglobulin®) – depleting

Timeline



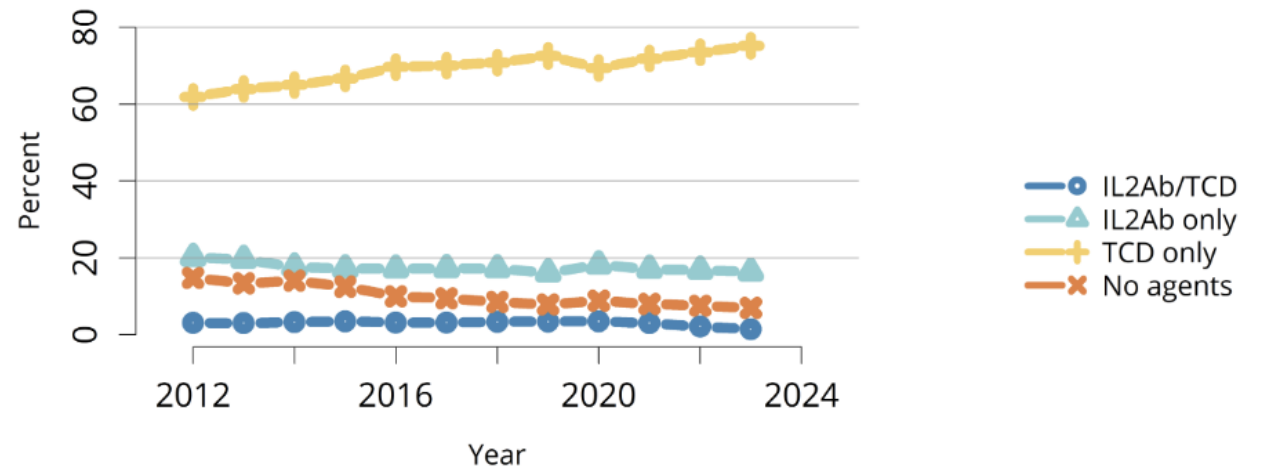
Use of Induction Agents

1: INDUCTION THERAPY

- 1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)
- 1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)
 - 1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (1B)
 - 1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)



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



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IL2Ab, interleukin-2 receptor antibody; TCD, T-cell depleting.

How do we define high immunologic risk?

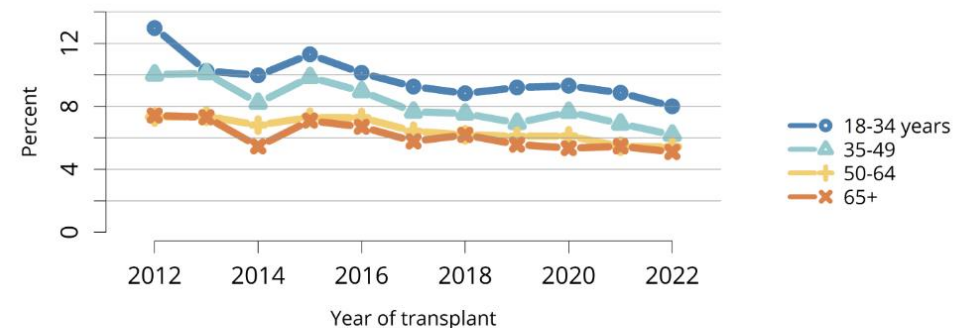
Immunologic factors

- PRA
- >1 transplant
- Donor specific antibodies
- HLA mismatches
- Ethnicity/race
- Baseline immunosuppression
- Age/Frailty

Non-immunologic factors

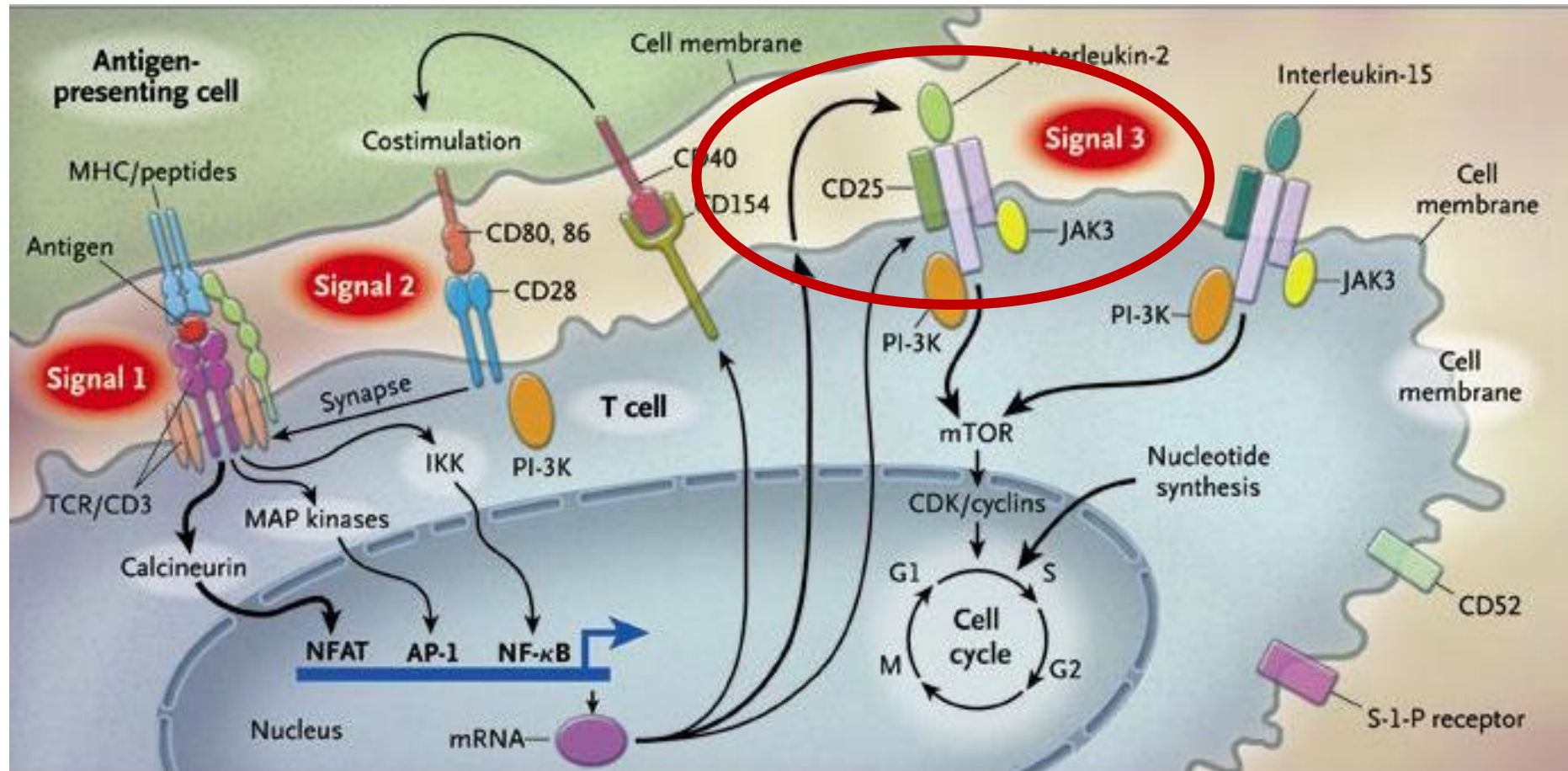
- CIT/ Delayed graft function
- Donor: KDPI >85; DCD
- Recipient: recurrent native disease; comorbidities
- Age/Frailty

Figure KI 67: Incidence of acute rejection by 1 year posttransplant among adult kidney transplant recipients by age



Non-Depleting: Basiliximab

- IL-2 receptor antagonist



Basiliximab

Points of Discussion	Basiliximab Characteristics
Dosing	<ul style="list-style-type: none">- 20 mg given pre-op, then 20 mg on POD4
Monitoring	<ul style="list-style-type: none">- No Therapeutic Drug Monitoring (TDM)- Clinical Monitoring: Hypersensitivity reactions have been observed
Duration of Activity	<ul style="list-style-type: none">- \geq[0.2 mg/L] provide significant IL-2 receptor saturation.- Doses from 20 to 60 mg yield receptor-saturating concentrations for up to 8 weeks post-transplant.- A cumulative dose of 40 mg preferred.
Place in Therapy	<ul style="list-style-type: none">- Only FDA approved agent for induction until 2017- Decreased rejection rates compared to placebo or cyclosporin-based regimens- Appropriate alt for low immunologic risk patient or patient w/ intolerance to depleting agents



Depleting: Anti-thymocyte globulins (horse and rabbit)

The anti-thymocyte globulins (ATG) are purified gamma globulin obtained by immunizing an animal w/ human thymocytes.

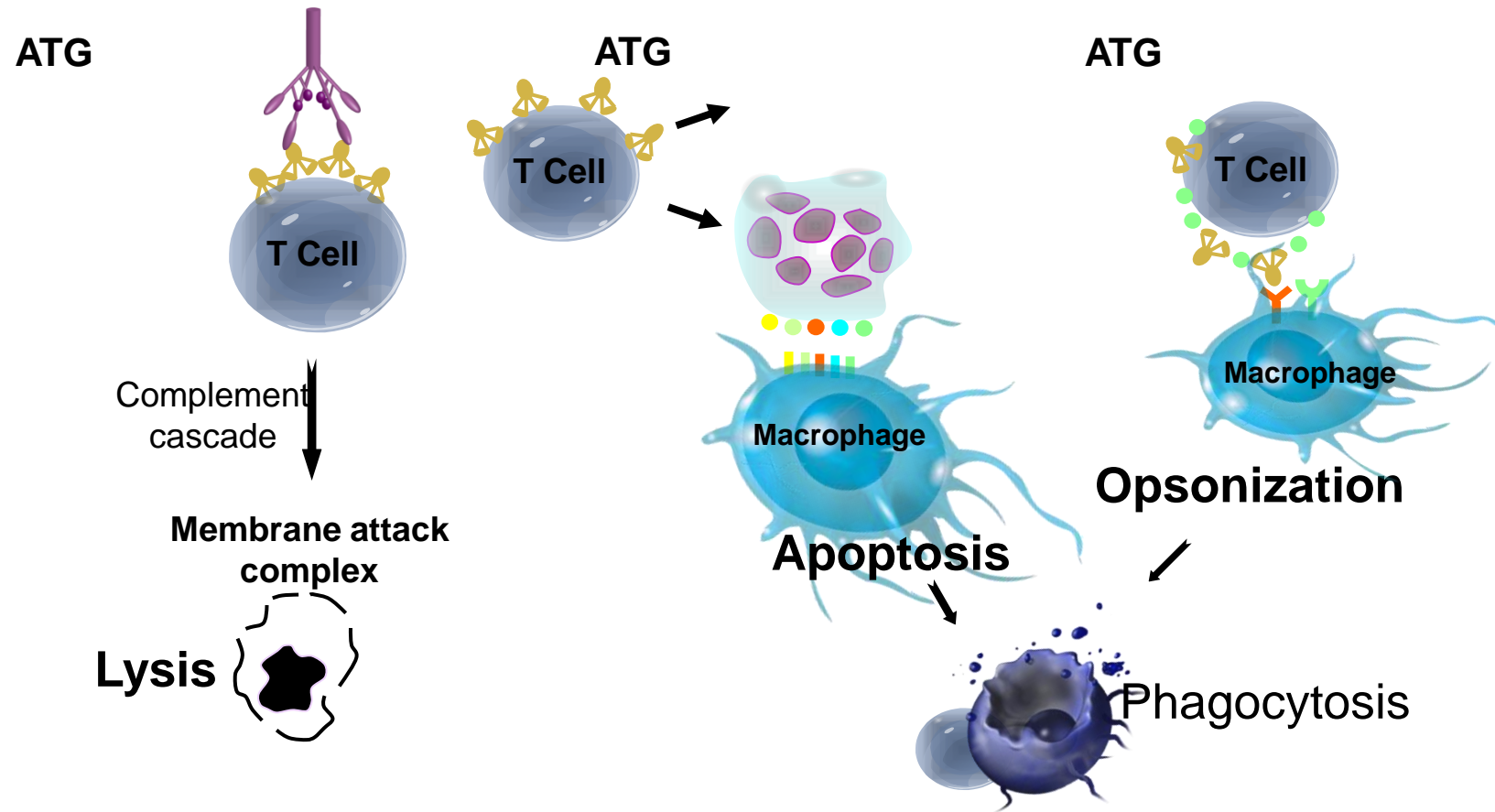
- Cytotoxic antibodies directed against a broad array of surface antigens expressed on T- and B-cells

Immune Response Antigens		Adhesion & Cell Trafficking	Heterogeneous Pathways
CD1a	CD28*	CD6	CD2
CD3/TCR	CD30	CD11a/CD18 (LFA-1)	CD5
CD4	CD32	CD44	CD11b
CD6	CD40	CD49/CD29 (VLA-4)	CD29
CD7	CD80*	CD50 (ICAM-3)	CD38
CD8	CD86	CD51/61	CD40
CD16	CD152 (CTLA-4)	CD54 (ICAM-1)	CD45
CD19	HLA class I	CD56*	CD52
CD20*	HLA DR	CD58 (LFA-3)	CD95
CD25*	β2-M	LPAM-1(α4β7)	CD126
		CD102 (ICAM-2)	CD138
		CD195 (CCR5)	
		CD197 (CCR7)	
		CD184 (CXCR4)	

Ankersmit HJ, et al. *Am J Transplant*. 2003;3:743. Bourdage JS, et al. *Transplantation*. 1995;59:1194. Michallet M-C, et al. *Transplantation*. 2003;75:657. Monti P, et al. *Int Immunopharmacol*. 2003;3:189. Pistillo MP, et al. *Transplantation*. 2002;73:1295. Prévile X, et al. *Transplantation*. 2001;71:460. Rebellato LM, et al. *Transplantation*. 1994;57:685. Tsuge I, et al. *Curr Ther Res*. 1995;56:671. Zand M, et al. *Transplantation*. 2005;79:1507. Zand MS, et al. *Blood*. 2006;107:2895.



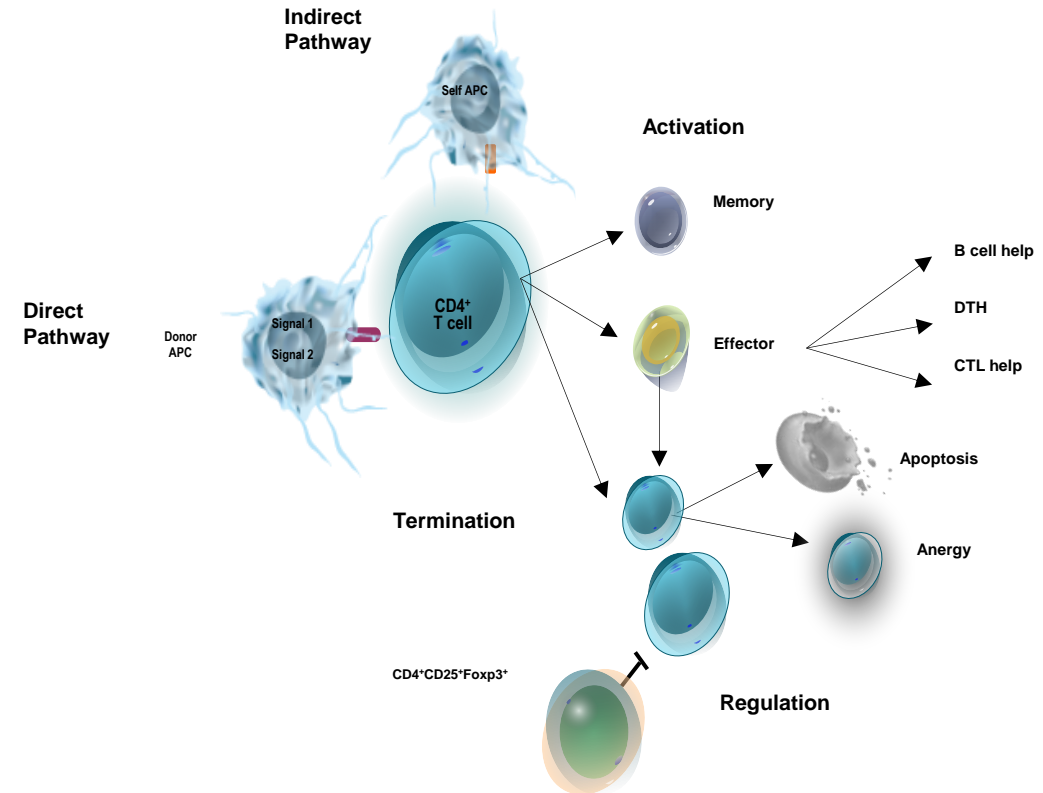
Anti-thymocyte globulins



Anti-thymocyte globulins

Immunomodulation

- Immune reconstitution generally occurs within 2-4 months, but can persist for years.
- rATG-mediated long term suppression partially attributed to the generation of regulatory T-cells.
- In vitro, rATG has the unique ability to convert $CD4^+CD25^-$ T-cells into $CD4^+CD25^+$ T-cells within 24 hrs.



Anti-thymocyte Globulins (Horse and Rabbit)

Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Dosing	<ul style="list-style-type: none"> - Cumulative doses of 3-6 mg/kg, generally given in doses of 0.75-1.5 mg/kg/day x 1-8 doses 	<ul style="list-style-type: none"> - 5-15 mg/kg/day for 4-14 days
Contraindication	<ul style="list-style-type: none"> - Allergy to rabbit proteins or serum 	<ul style="list-style-type: none"> - Allergy to horse proteins or serum
Monitoring	<ul style="list-style-type: none"> - No TDM, but some centers monitor T-cell depletion <ul style="list-style-type: none"> - WBC (ALC $<200/\text{mm}^3$) or CD3^+ T-cells ($<20/\text{mm}^3$) - Clinical Monitoring: <ul style="list-style-type: none"> - Infusion-related reactions - Immune-mediated reactions - Myelosuppression <ul style="list-style-type: none"> - WBC 2-3 K = $\frac{1}{2}$ dose; < 2 K = hold/discontinue - Plts 50-75 K = $\frac{1}{2}$ dose; <50 K = hold/discontinue 	<ul style="list-style-type: none"> - No TDM - Clinical Monitoring: <ul style="list-style-type: none"> - Stop infusion immediately if a systemic reaction or anaphylaxis occurs. - Other infusion-related or immune-mediated reactions - Myelosuppression
Duration of Activity	<ul style="list-style-type: none"> - $t_{1/2}$ = 2-3 days - ~3 months before immune reconstitution. 	<ul style="list-style-type: none"> - $t_{1/2}$ = 6-9 days - ~3 months before immune reconstitution.
Place in Therapy	<ul style="list-style-type: none"> - Most commonly used induction agent <ul style="list-style-type: none"> - High immunologic risk - Delayed CNI initiation - IS minimization or withdrawal - Only FDA approved in kidney txp since 2017 	<ul style="list-style-type: none"> - Allergy/CI to rATG - Only FDA approved for rejection (not induction)

Equine (eATG) v rabbit (rATG) thymoglobulin

Efficacy: rATG w/ significantly lower rates of BPAR and improved allograft/patient survival at 1-, 5- and 10-years

Safety: rATG w/ significantly lower rates of CMV infection, despite higher early rates of leukopenia. Similar rates of PTLD.



Basiliximab v rATG in “high risk” recipients

- 278 pts at elevated risk (PRA >20%, retransplant, high risk for DGF) given rATG x4 or basiliximab x2 and triple maintenance IS (CsA based)
- Efficacy: Similar composite end point of BPAR, DGF, allograft/patient survival. No difference in graft loss or death.
 - rATG w/ significantly lower rates of BPAR (15.6% v 25.5%; $p=0.02$) and AR requiring Ab rx (1.4% v 8%; $p=0.005$)

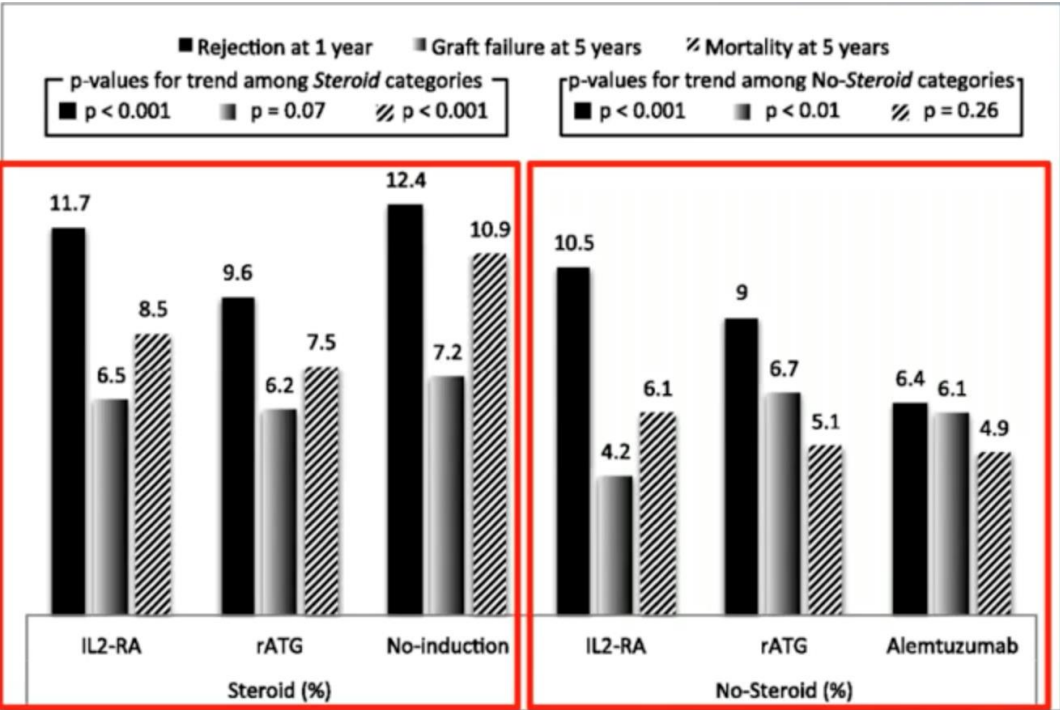
Safety: rATG w/ significantly higher rates of myelosuppression and overall infections

- rATG w/ significantly fewer cases of CMV, despite higher early rates of leukopenia.



What about “low-risk” recipients (living donors)?

- Living donor recipients on TAC/MMF +/- steroids on d/c (n=36,153)
- TAC/MMF/steroids (n=25,996): IL2RA v rATG v no induction
 - No benefit to IL2RA; lower AR w/ rATG but same graft survival
- TAC/MMF no steroids (n=10,157): IL2RA v rATG v alemtuzumab
 - Lower AR w/ depleting Ab; higher graft loss w/ alemtuzumab



1y Rejection: PS-weighted logistic regression:

Induction Type	OR (95% CI)	P
Steroid:		
IL-2 RA	1	
r-ATG	0.78 (0.70 to 0.88)	<0.001
No induction	0.96 (0.86 to 1.08)	0.48
No Steroid:		
IL-2 RA	1	
r-ATG	0.73 (0.59 to 0.90)	0.004
Alemtuzumab	0.53 (0.42 to 0.67)	<0.001

Graft loss: PS-weighted logistic regression:

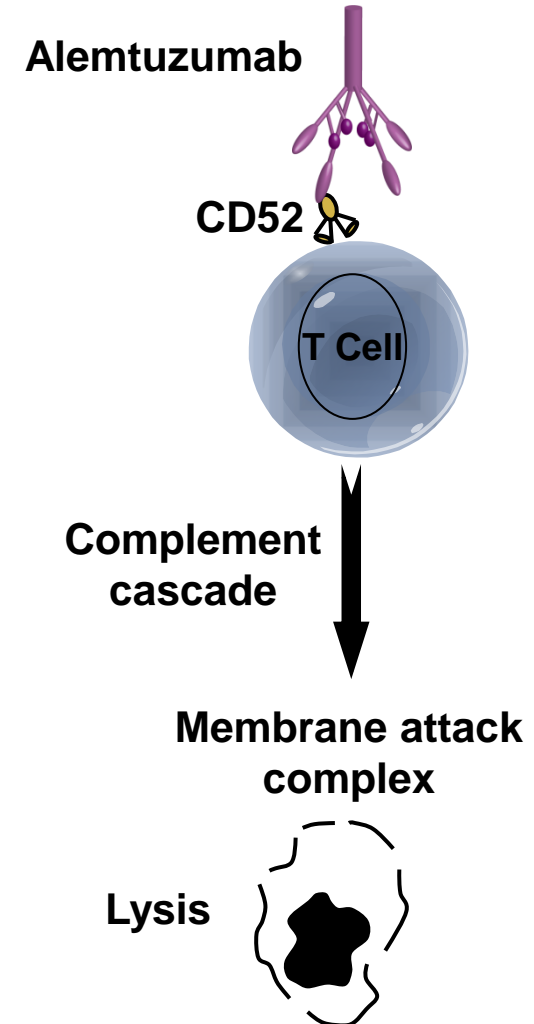
Induction Type	OR (95% CI)	P
Steroid:		
IL-2 RA	1	
r-ATG	0.99 (0.91 to 1.08)	0.79
No induction	0.99 (0.90 to 1.08)	0.76
No Steroid:		
IL-2 RA	1	
r-ATG	1.19 (0.97 to 1.45)	0.01
Alemtuzumab	1.27 (1.03 to 1.56)	0.02

Tanriover et al. CJASN 2015; 10:1041-1049



Depleting: Alemtuzumab

- anti-CD52 humanized, monoclonal Ab
 - FDA indication in B-cell CLL and multiple sclerosis.
- CD52 is present on virtually all B- and T-cells, as well as macrophages, NK cells and some granulocytes.
- The alemtuzumab-CD52 complex triggers antibody-dependent lysis.



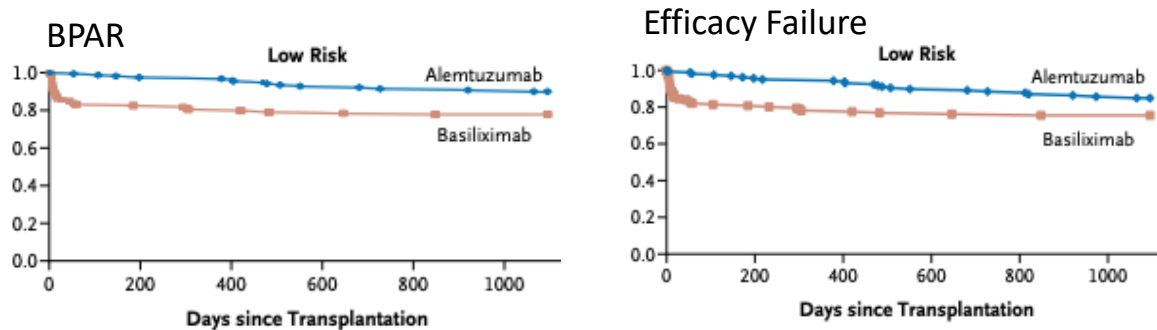
Alemtuzumab

Points of Discussion	Alemtuzumab Characteristics
Dosing	<ul style="list-style-type: none"> - 30 mg given as a single dose intra-op
Monitoring	<ul style="list-style-type: none"> - No TDM, but some centers will monitor the long-term effects of alemtuzumab by monitoring CD4⁺ counts - Clinical Monitoring: <ul style="list-style-type: none"> - Infusion-related reactions (i.e., nausea, vomiting, diarrhea, headache, dyesthesias and dizziness) - Immune-mediated reactions (i.e., fever, chills, hypotension, tachycardia, edema, myalgia) - Myelosuppression
Duration of Activity	<ul style="list-style-type: none"> - several months, in some cases > 1 year for immune reconstitution
Special Considerations	<ul style="list-style-type: none"> - Clinical Considerations <ul style="list-style-type: none"> - significant IL-21-driven autoimmune response during immune-reconstitution -> higher rate of AMR compared to rATG (Noureldeen et al). - Distribution <ul style="list-style-type: none"> - As of 2012, alemtuzumab is no longer commercially available -> Campath Distribution Program free of charge.
Place in Therapy	<ul style="list-style-type: none"> - Use >1 dose can result in prolonged leukopenia and increased risk of severe infection - IS minimization or withdrawal - Cost saving initiative – free drug and early discharge - Not FDA approved – off label use



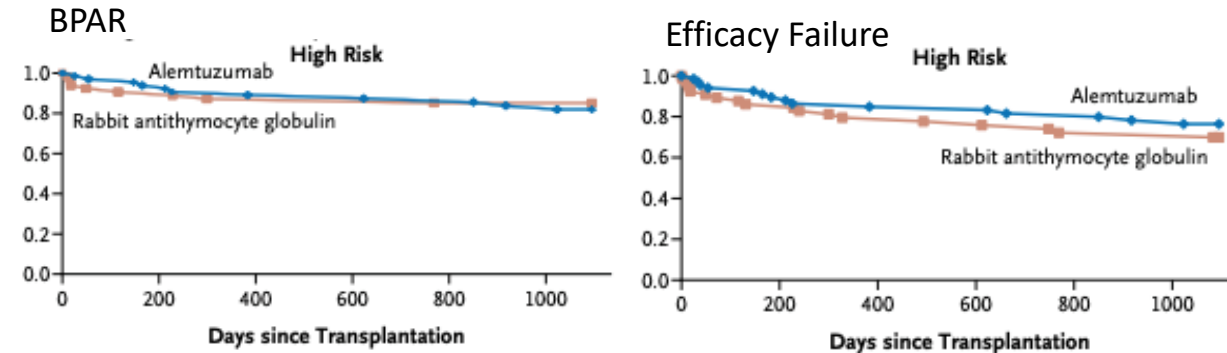
Alemtuzumab vs. Basiliximab (low-risk); vs. rATG (high-risk) -> INTAC study

Low risk (n=335)



- Lower incidence of BPAR compared to IL-2RA
- Composite endpoint (no rejection, graft loss or death) significantly better.
- Late rejection (BPAR 12-36 months) -> numerically higher rates w/ alemtuzumab (8% vs. 3%; p=ns).
*not adequately powered.
- SAFETY: lower rates of serious infectious complications w/ IL-2RA

High Risk (n=139)



- BPAR similar post-txp.
- Composite endpoint was similar.
- Late acute rejection was numerically more common with alemtuzumab (10% vs. 2%; p=NS)
- SAFETY: overall, more infectious disease seen with rATG, but similar rates of serious infectious complications.

- No differences in mortality, GS or GFR among groups
- Study performed with steroid withdrawal.



Poll Question:

- Continuation of Induction Case:
- Nadir SCr was 1.93 at 3 month post-txp
- Renal biopsy showed severe arteriosclerosis that may explain why his SCr remains high.
- TAC 8-10 ng/dl before the biopsy
- MPA 720 mg BID; no corticosteroids

What would you do with Maintenance Immunosuppression:

1. Continue the current immunosuppression course
2. Drop TAC goal to 6-8 ng/dl and add back in 5 mg of Prednisone
3. Convert patient from TAC to Everolimus
4. Convert patient from TAC to Belatacept



Maintenance Immunosuppression

Calcineurin Inhibitors (CNI)

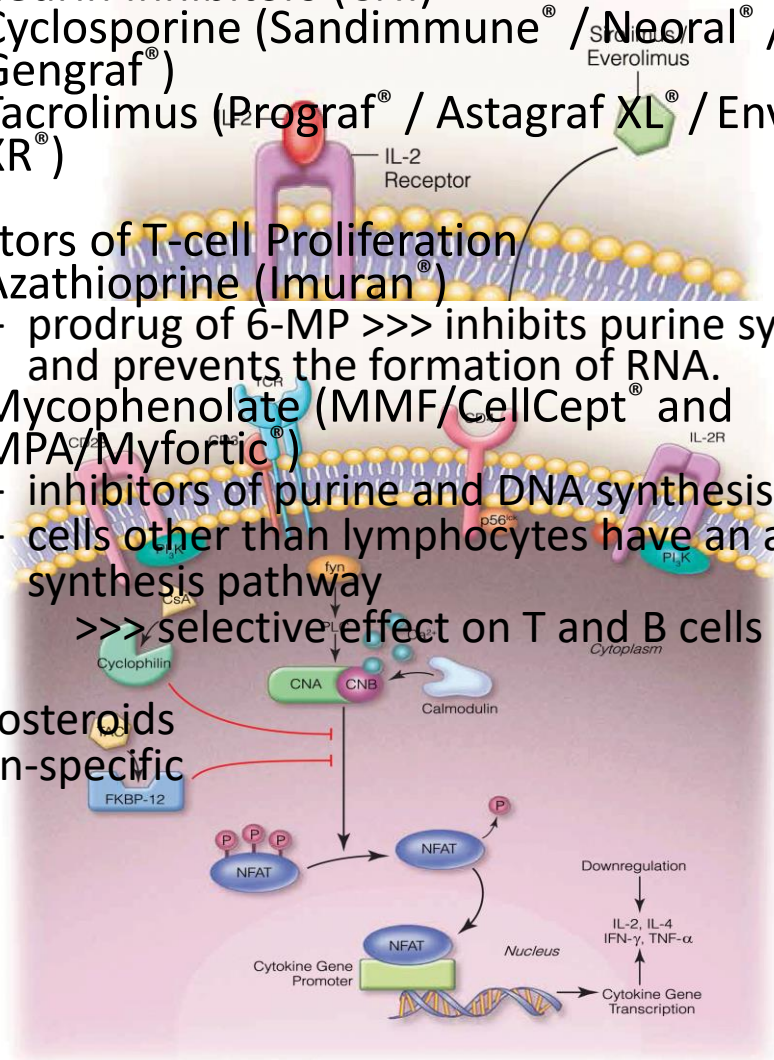
- Cyclosporine (Sandimmune® / Neoral® / Gengraf®)
- Tacrolimus (Prograf® / Astagraf XL® / Envarsus XR®)

Inhibitors of T-cell Proliferation

- Azathioprine (Imuran®)
 - prodrug of 6-MP >>> inhibits purine synthesis and prevents the formation of RNA.
 - Mycophenolate (MMF/CellCept® and MPA/Myfortic®)
 - inhibitors of purine and DNA synthesis
 - cells other than lymphocytes have an alternate synthesis pathway
- >>> selective effect on T and B cells

Corticosteroids

- Non-specific

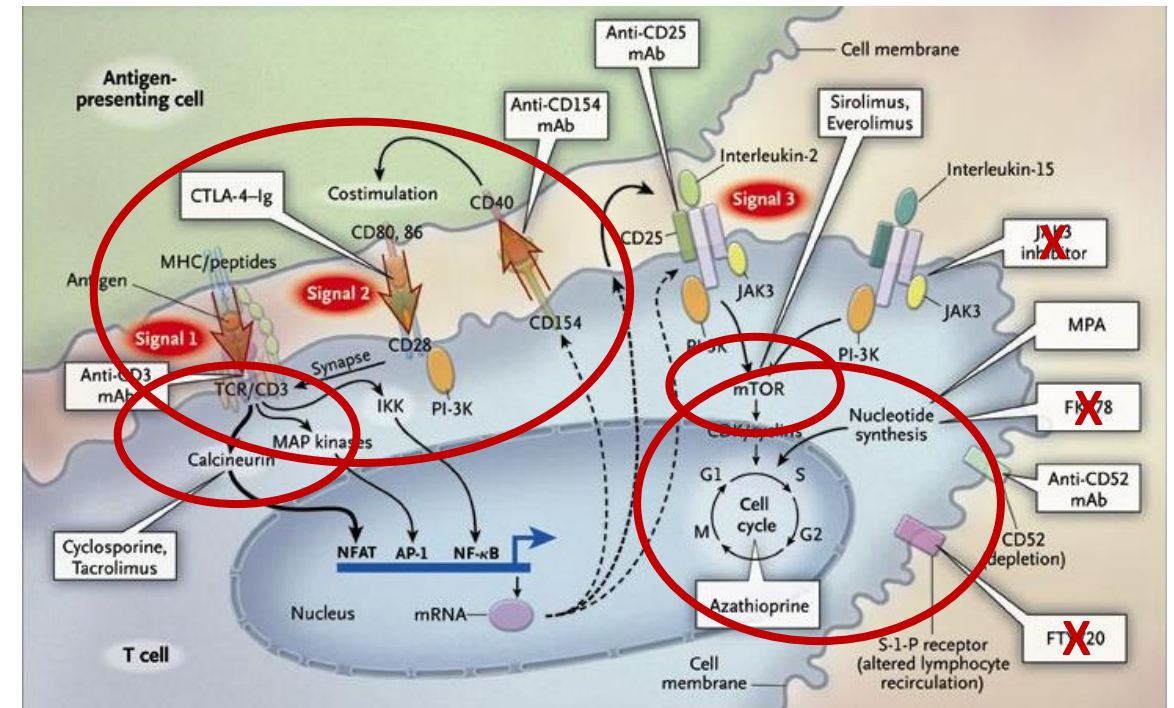


Mammalian Target of Rapamycin (mTOR) Inhibitors

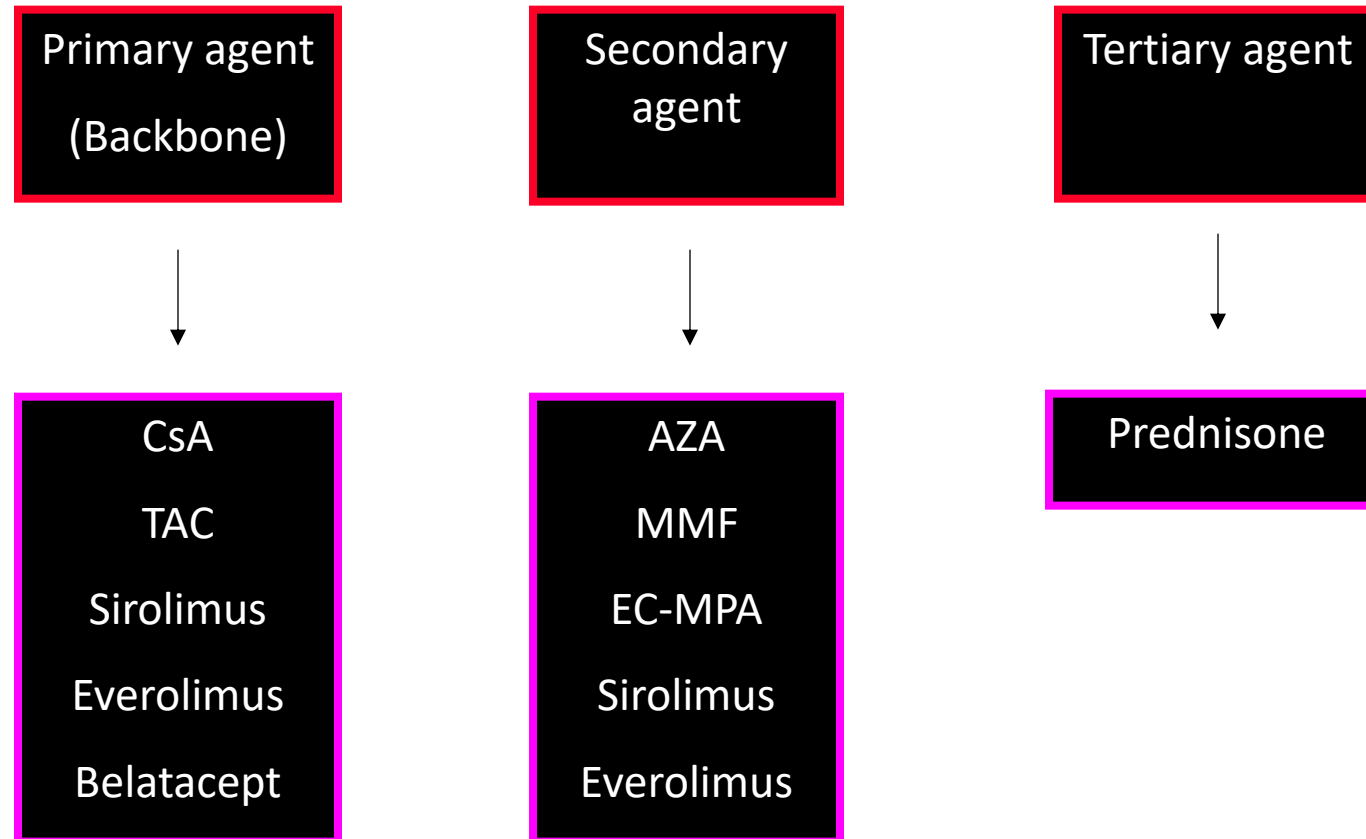
- Sirolimus (Rapamune®) and Everolimus (Zortress®)

Co-Stimulation Blockade

- Belatacept (Nulojix®)



Common Combinations of Immunosuppressive Regimens

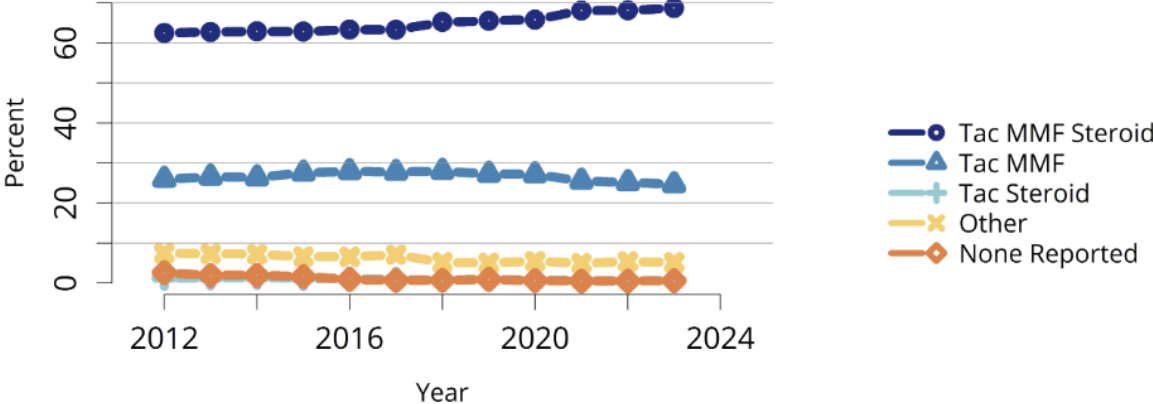


AZA = azathioprine, CSA = cyclosporine, EC-MPA=enteric-coated mycophenolate sodium, MMF = mycophenolate mofetil, TAC = tacrolimus



Use of Maintenance Immunosuppression

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



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2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)

2.2.1: We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B)

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)

2.5: We recommend that if mTORi are used, they should not be started until graft function is established and surgical wounds are healed. (1B)

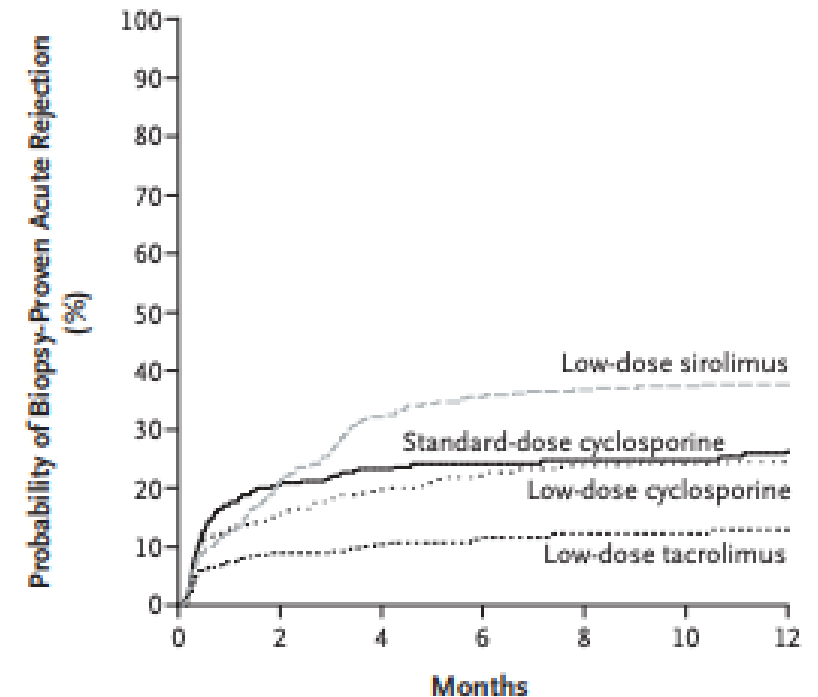
CNI, calcineurin inhibitor; CsA, cyclosporine A; mTORi, mammalian target of rapamycin inhibitor(s).



The Symphony Trial: Defining the “Gold Standard”

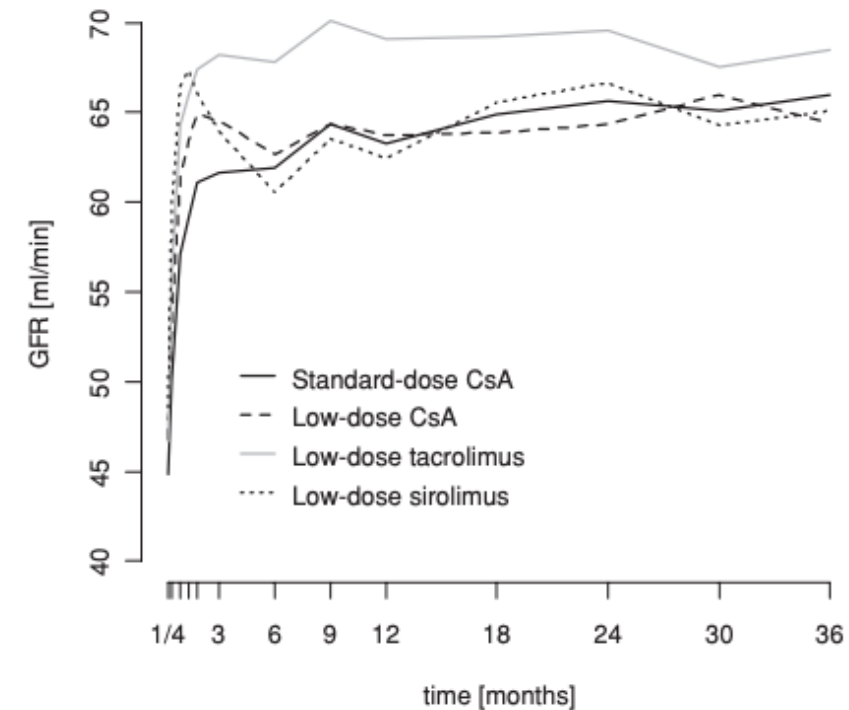
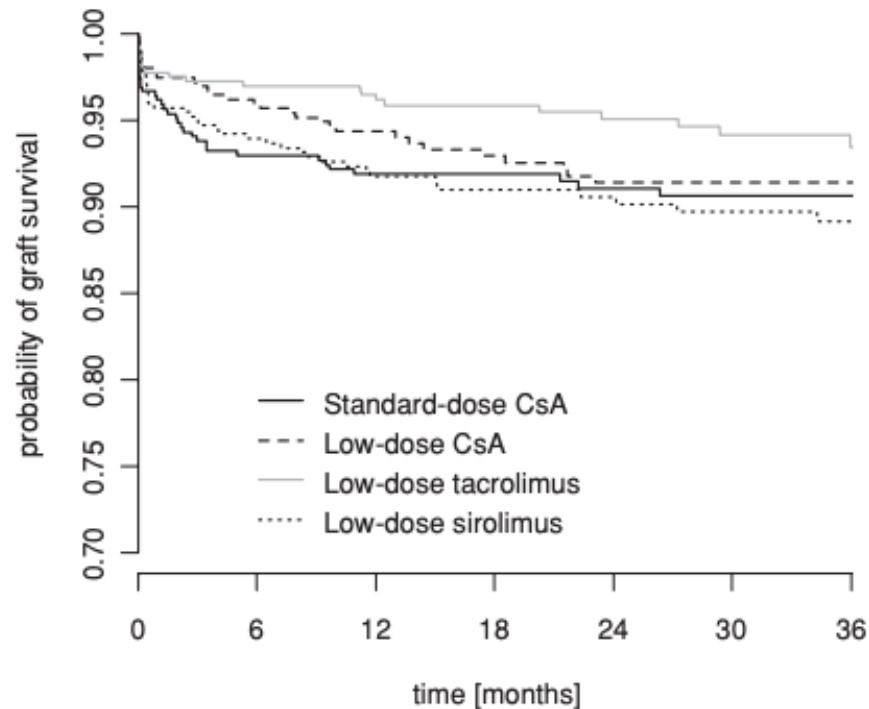
- Randomized open-label multicenter trial (n=1,645)
- 4 treatment arms (+ MMF/pred)
 1. CsA 150-300 ng/m x3 mo, then 100-200
 2. CsA 50-100 ng/mL (IL2RA induction)
 3. TAC 3-7 ng/mL (IL2RA induction)
 4. SRL 4-8 ng/mL (IL2RA induction)

Regimen	Acute rejection (%)	Graft survival (%)	GFR (mL/min)
CsA “standard”	25.8	89.3	57.1
CsA “low”	24	93.1	59.4
TAC “low”	12.3	94.2	65.4
SRL “low”	37.2	89.3	56.7



How much tacrolimus? – Symphony 3-yr follow-up

Drug trough	TAC (3-7)	CsA (100-200)	CsA (50-100)	SRL (4-8)
12 mo	6.4	142	101	7.5
36 mo	6.5	114	103	7.0



History of CNIs

- CsA introduced in human trials 1978 -> approved 1993
- TAC first used in 1991 -> approved for use in liver transplant in 1994
 - Soon became preferred CNI
 - less inter-patient variability, better oral bioavailability and better correlation of trough lvls with AUC
- Early use of CNI were hindered by excessive toxicity due to high levels
 - CNI-related nephrotoxicity -> drive to minimize or avoid use
 - Use of adjunctive agents allowed for lower target levels
 - Desire to avoid CNIs led to development of donor specific antibodies
- TAC remains backbone of most IS regimens



Calcineurin Inhibitors: CsA and TAC

Numerous studies have compared efficacy and side-effects.

Efficacy

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

DDI: both agents are substrates for CYP3A4, CYP3A5 and P-gp

Dosing:

- Significant inter- and intra-patient variability -> therapeutic drug monitoring (TDM)
 - CsA and TAC: overall exposure is best correlated to C_0 levels
- Appropriate levels are dependent on institution-specific protocols and concomitant immunosuppressants (long term trough goal 5-8)

Safety/tolerability

- CsA -> greater increases in lipid levels and blood pressure
- TAC -> greater incidence of new-onset post-transplant diabetes (PTDM) and neurologic adverse events
- Each has drug-specific side-effects



CNI Adverse Events

- Cardiovascular – Hypertension; Hypercholesterolemia
- Glucose intolerance
- Neurotoxicity – Tremor; Headache; Insomnia; Paresthesia
- Nephrotoxicity – perhaps long-term dose and level-related
- Malignancy – related to overall immunosuppression
- Physical – Gingival Hypertrophy; Hirsutism (CSA); Alopecia (TAC)



Envarsus (LCPT) vs. Prograf

- Phase 3 double-blind randomized trial
- 543 KTR randomized to Envarsus vs Prograf
- Similar efficacy (AR, graft loss, patient survival)
- Similar trough levels except first 2 weeks (higher w/ envarsus)
 - LCPT dose reduced 20-30%
- eGFR equivalent between groups throughout 2 yrs

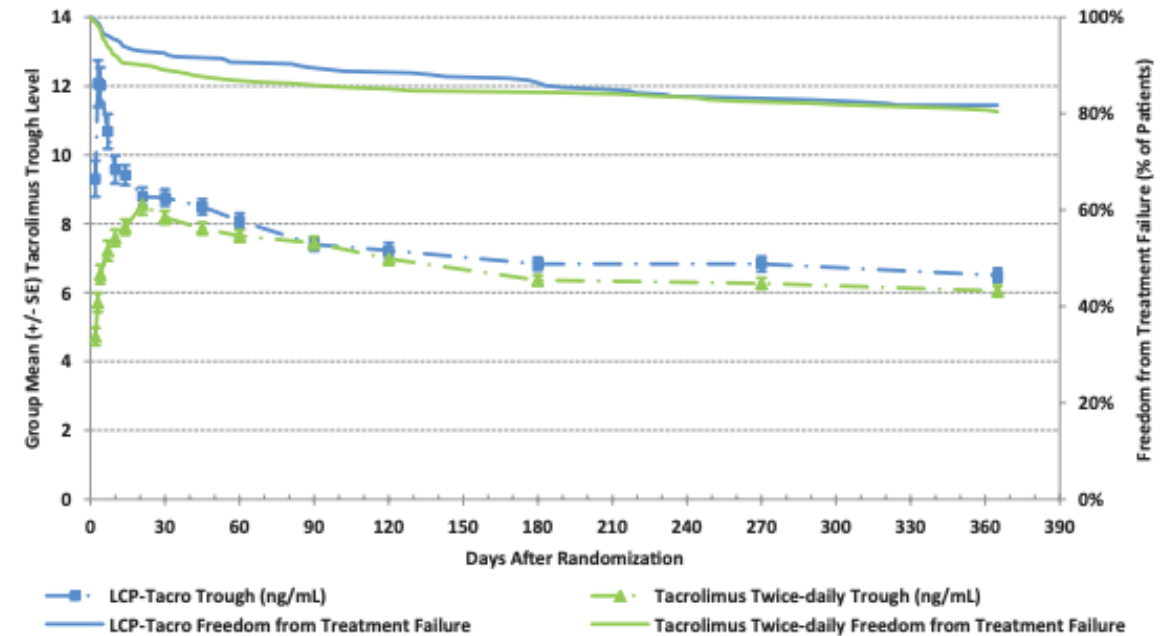
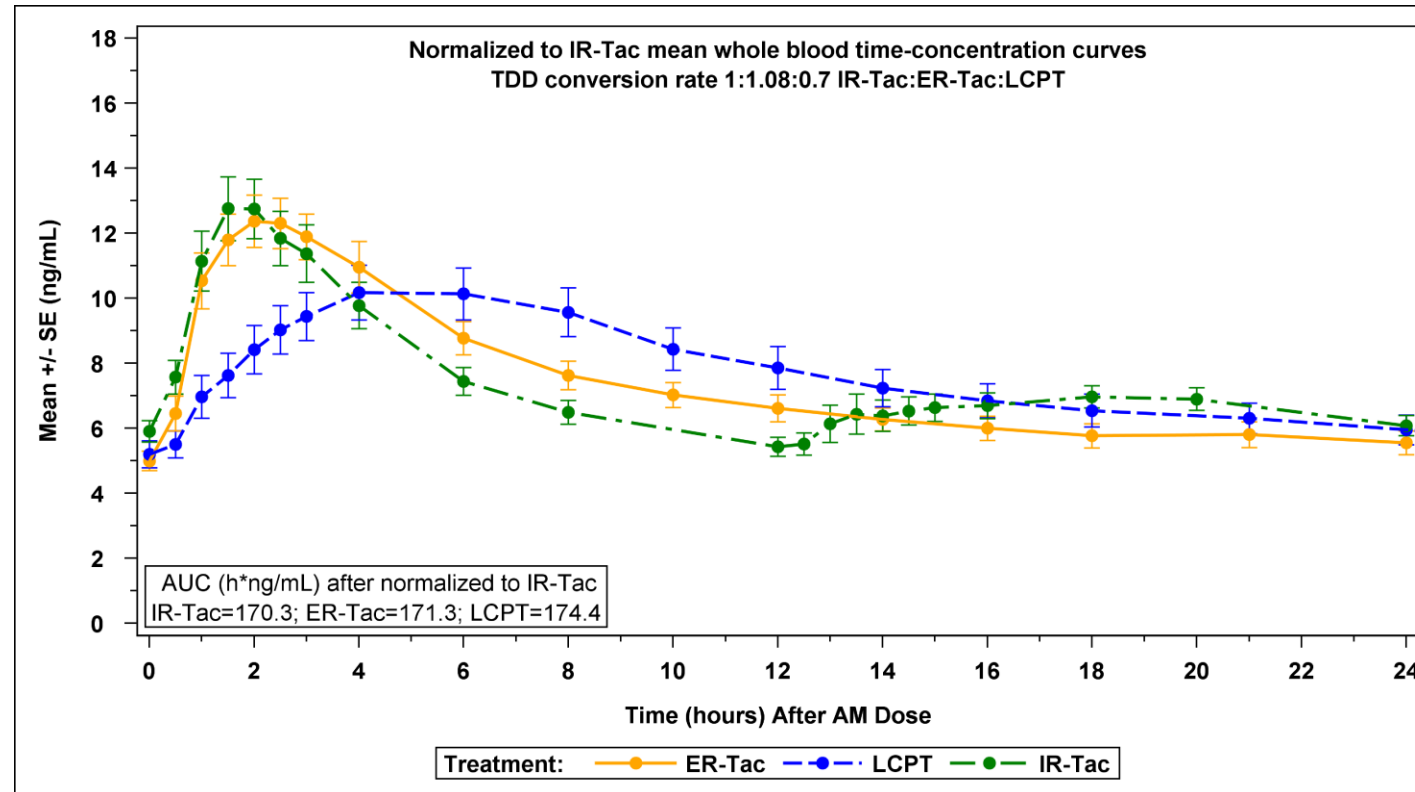


Figure 2: Mean tacrolimus trough levels and Kaplan-Meier freedom from treatment failure over the study period, LCP-Tacro versus tacrolimus twice-daily.

IR Tac (Prograf) vs. Tac-ER (Astagraf XL) vs. LCP-Tac (Envarsus XR)



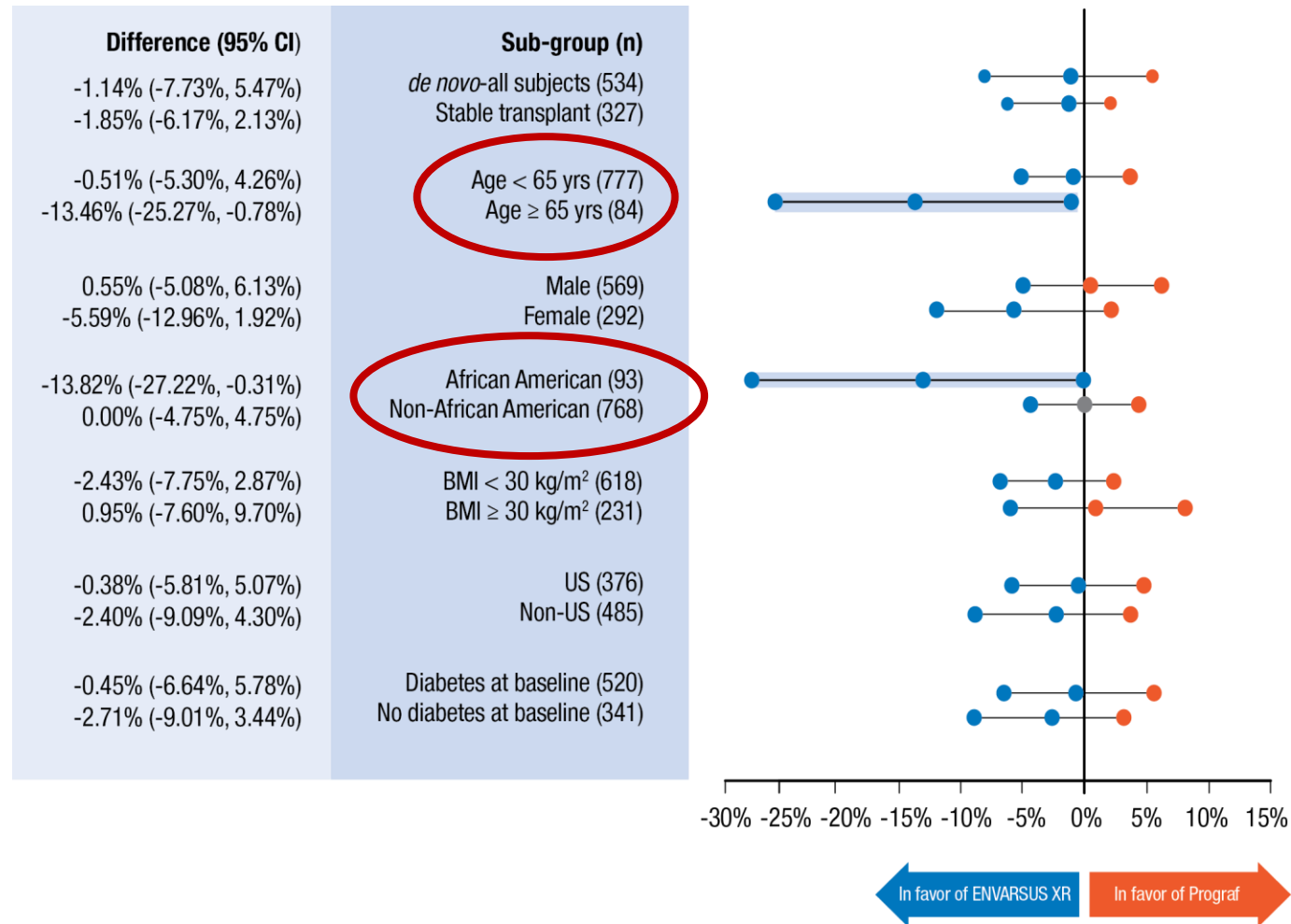
- Both TAC-IR and TAC-ER exhibited similar PK profiles with higher peak concentrations, shorter time to T_{max} , and higher peak-trough ratio compared with LCP-TAC when normalized for AUC

Tremblay S, et al. *American Journal of Transplantation*. 2017;17(2):432-442.

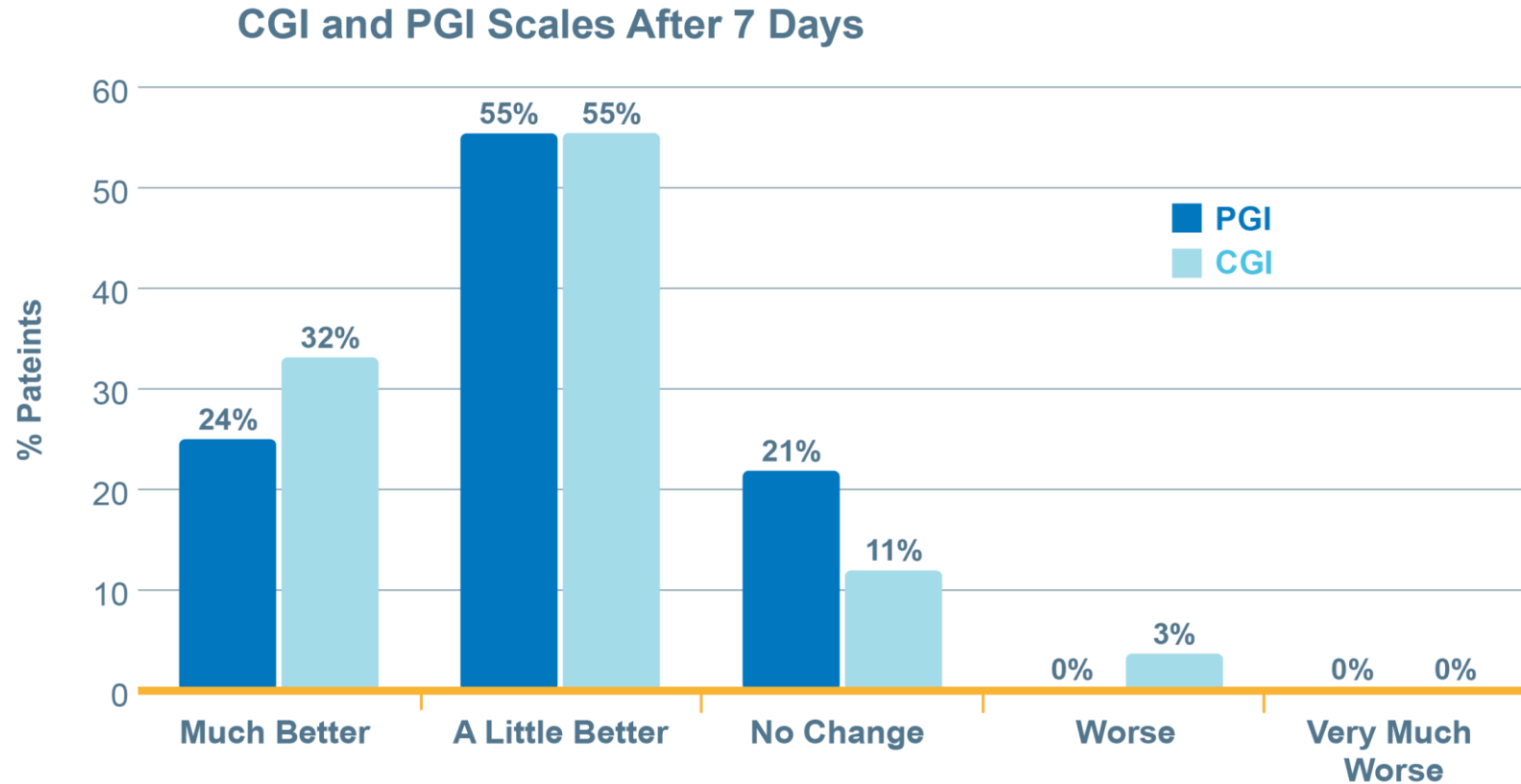


Who may benefit from Envarsus?

Treatment Failure at 1 year



Which do patients prefer?



- 78.9% of patients and 86.8% of physicians reported an improvement after switching to LCP-Tacro ($P < 0.0005$ and $P < 0.0001$, respectively)



Mycophenolate: MMF and EC-MPA

Dosing:

- MMF: 1 g BID
- EC-MPA: 720 mg BID
 - TDM is not routinely recommended

DDI: divalent/trivalent cation-containing antacids and supplements, CsA

- MMF only appears to interact with proton pump inhibitors¹

ADR:

- Myelosuppression
- Gastrointestinal disorders, both upper and lower GI tract
- Associated with significant teratogenic effects (REMS program with all MPA products)



Azathioprine

Dosing: 1 - 3 mg/kg/day, titrated to hematological effects

DDI: allopurinol, febuxostat

ADR:

- Myelosuppression (typically more so than MMF/MPA)
- RARE: pancreatitis

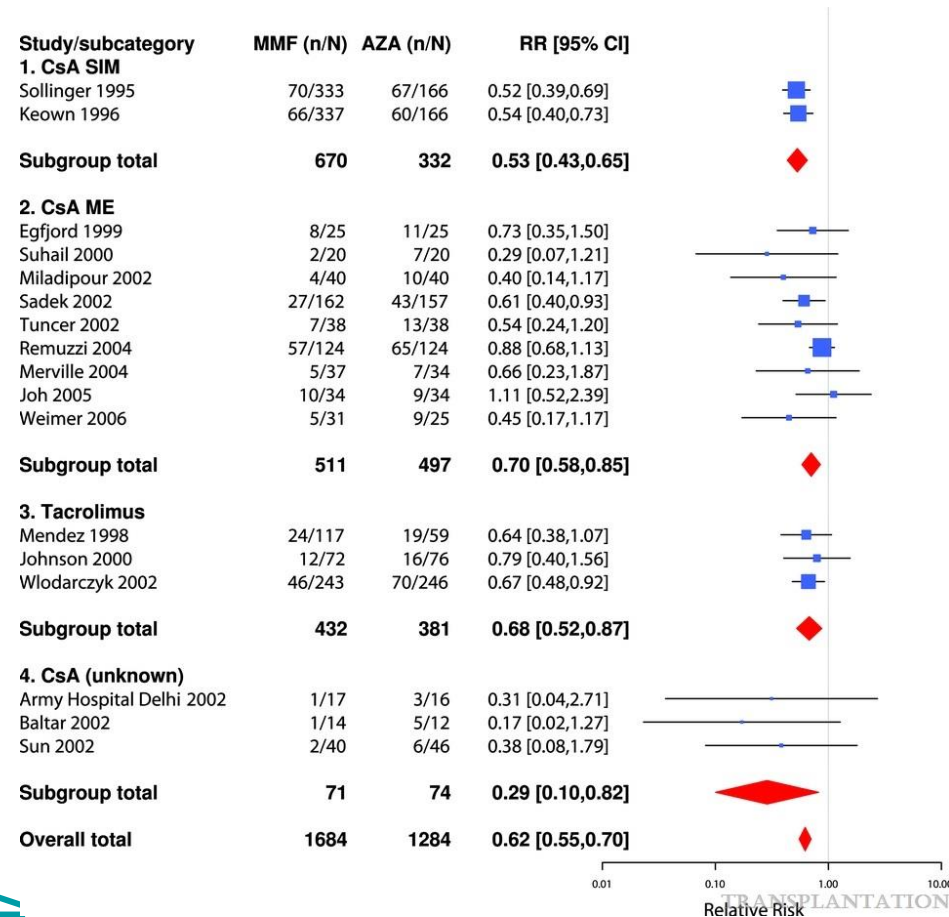


MMF vs AZA

Meta-analysis of 19 RCTs comparing MMF to AZA

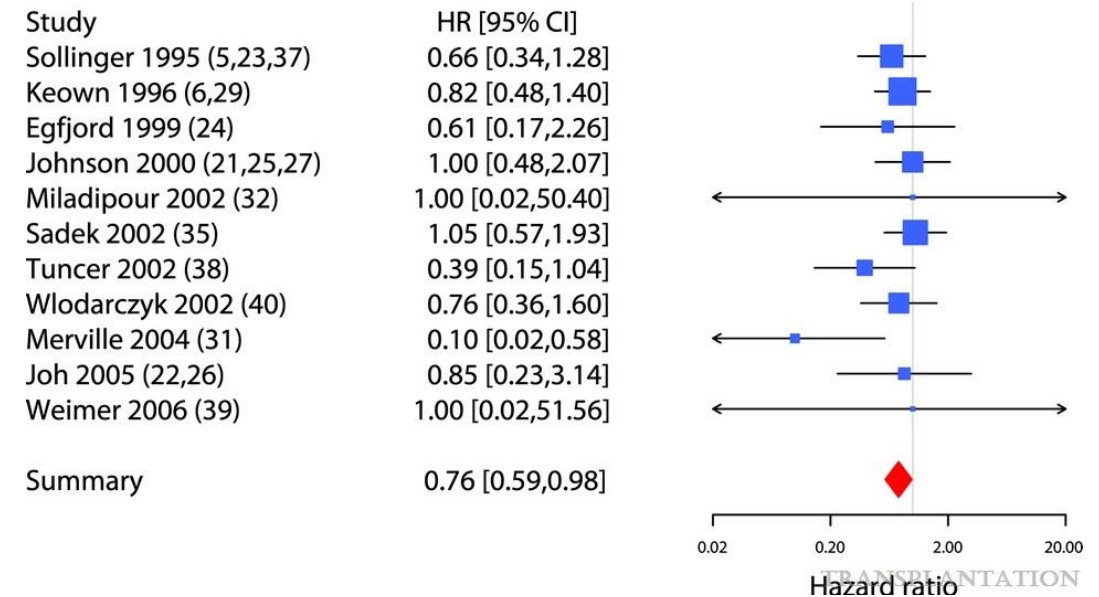
Acute rejection

- 38% reduction in risk w/ MMF



Graft loss

- 24% reduction in hazard for all-cause graft loss
 - Evidence is weak and finding is controversial
 - No evidence that MMF improves patient survival



Corticosteroids

The exact MOA is still not fully understood.

- High dose: > 100 mg of prednisone equivalents.
 - MOA = directly toxic to T cells
- Low dose: < 100 mg of prednisone equivalents.
 - nonspecific immunosuppressive agents - inhibit IL-1, IL-2, IL-3, IL-6, IL-15, TNF-alpha and INF-gamma at low doses.
 - Decreased activation of T cells.

What we do know:

- Blockade of Cytokine Gene Expression
 - ↓ T-cell and APC cytokine expression
 - Bind to heat shock protein → translocates to nucleus → binds to GRE → inhibits transcription of cytokine genes → inhibition of IL-1, IL-2, IL-3, IL-6, INF- γ , and TNF- α
 - ↓ cytokine-receptor expression
- Nonspecific Effects
 - Anti-inflammatory effects



Corticosteroids

Dosing: doses vary widely from institution to institution.

- Highest doses at time of transplant or as treatment of an acute rejection episode.

DDI: CYP - 450 inducer (dexamethasone) and inhibitor (methylprednisolone).

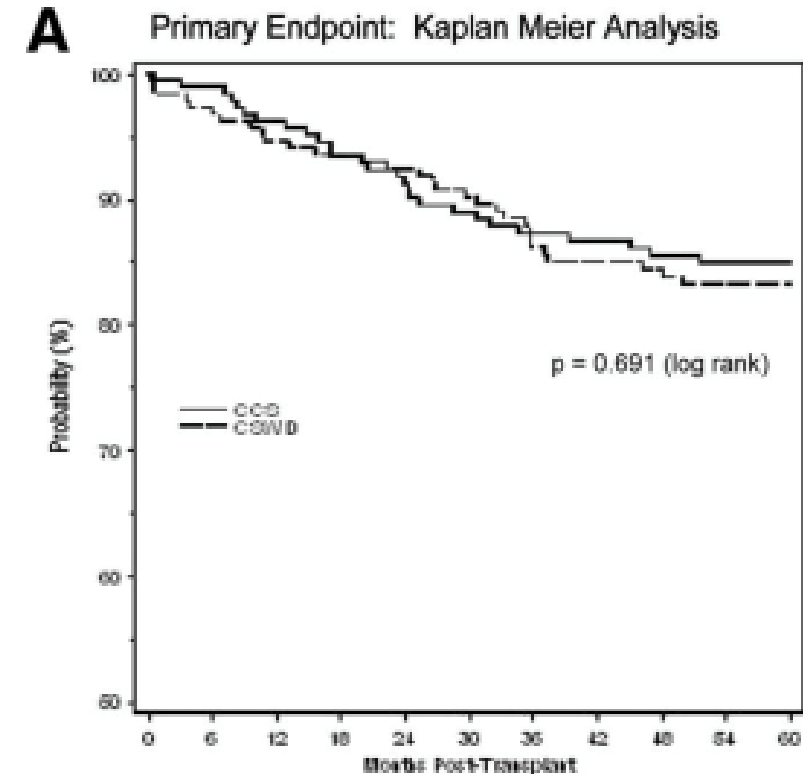
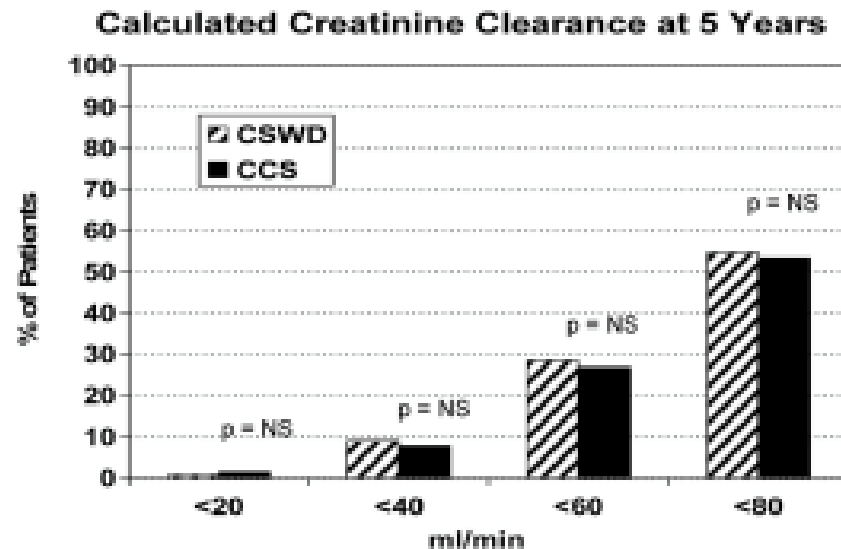
ADR:

- Cardiovascular (hypertension, hyperlipidemia)
- Endocrine (hyperglycemia)
- CNS (mood changes, anxiety)
- Osteoporosis
- Weight gain
- Edema
- Lipodistrophy

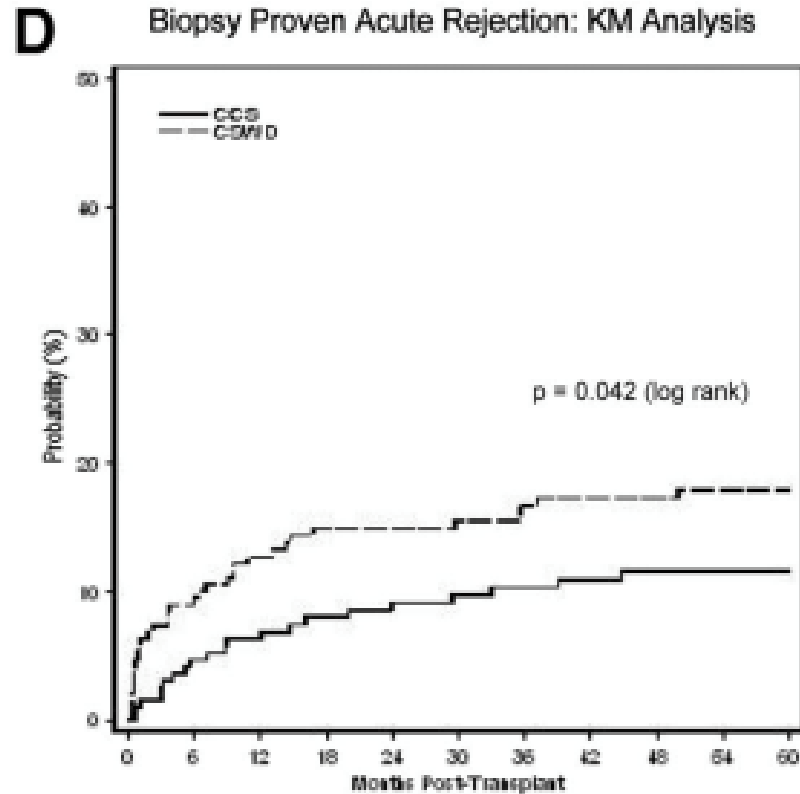


Early Corticosteroid Withdrawal

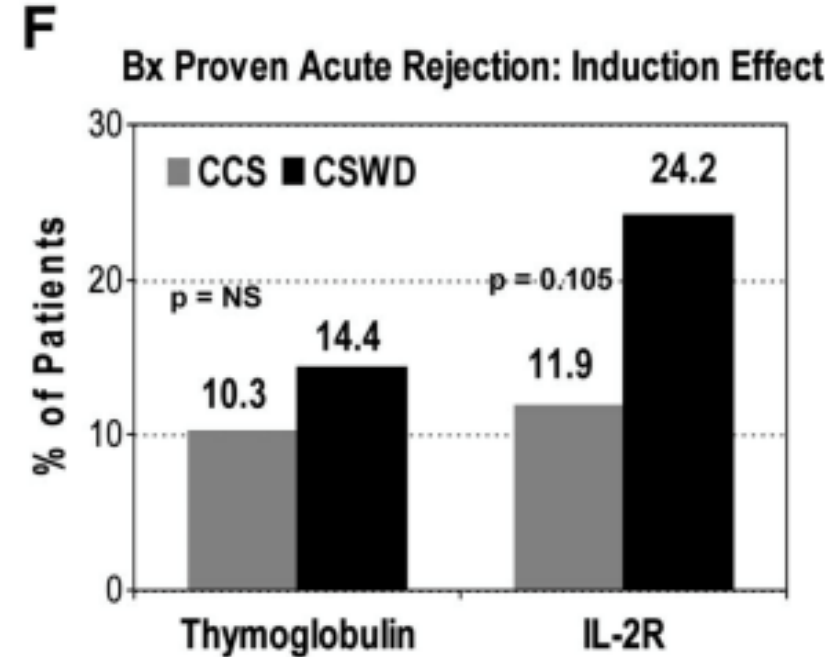
- 60 month randomized, controlled, double blind, double dummy multicenter trial (n=386)
- Two arms: TAC/MMF/pred vs TAC/MMF/steroid withdrawal within 7 days
- 5 yr follow-up:
 - Similar graft/patient survival w/wo pred
 - Similar CrCl @ 5 yrs (assessed by quartiles)



Early Corticosteroid Withdrawal and Acute Rejection



- Acute rejection rate @ 5 yr: CCS 10.8% vs CSWD 17.8%



- Steroid withdrawal: higher acute rejection rate, particularly w/ IL-2RA induction (24.2% vs 14.1%)
- Control Group: similar acute rejection rates (10.3% vs 11.9%) w/ either induction agent



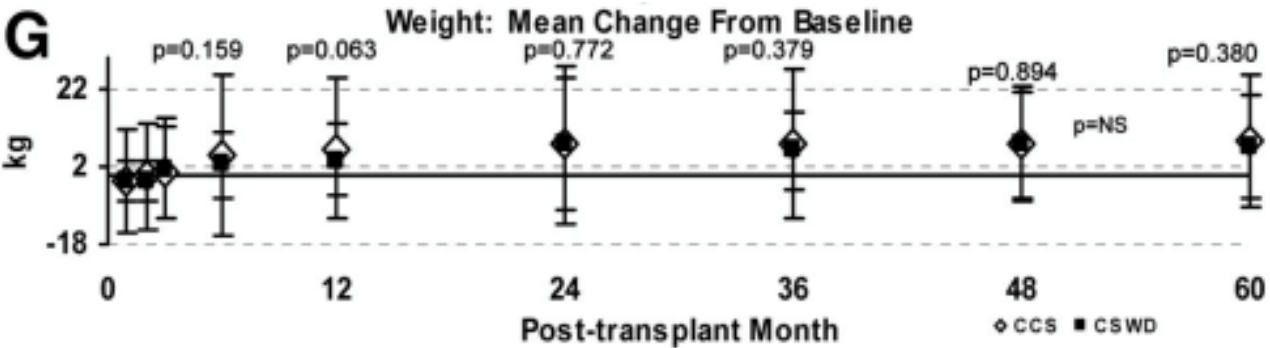
Early Corticosteroid Withdrawal: Additional Outcomes

- No difference in infections (including CMV, BKV), HTN, total cholesterol, Framingham risk score, cataract formation

- Bone Disease:

Bone complications					
Avascular necrosis	5	2.6	0	0.0	0.061
Fractures	19	9.7	10	5.2	0.122
Avascular necrosis and/or fractures	22	11.3	10	5.2	0.041

- Weight Gain:



Early Steroid Withdrawal Controversy

Why Not? (Pro CSWD)

- 5 yr outcomes (“primary endpoint”) comparable
- Marginal benefit in bone disease
- Use of insulin for new PTDM was less w/ CSWD (3.7% vs 11.6%, $p=0.05$)

Why?

- Higher risk of rejection
- Post-hoc analysis w/ moderately higher rates of chronic allograft nephropathy w/ CSWD (9.9% vs 4.1%, $p=0.028$).
- No difference in infections, HTN, wt gain, cholesterol, Framingham CV risk, or malignancy



“Late” Steroid Withdrawal

- Meta-analysis in CNI+MMF/MPA-based trials -> 9 trials, n=1519
- No difference in overall patient/graft survival
- Increased acute rejection (13.6% vs 5.8%) when withdrawing pred 3-6 months post-transplant
 - 7/9 CSA-based show increased RR for AR of 1.61
 - 2/9 TAC-based show no increased risk -> only 62% of CSWD remained steroid free at 3 yrs

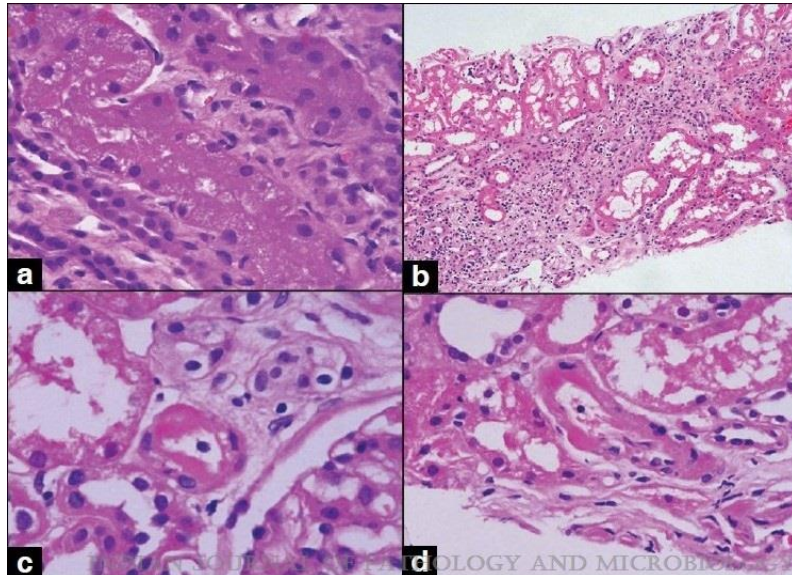
Trials	n	Multicenter trial	Treatment			Control Conventional therapy	Follow-up period (mo)	Completeness of follow-up (%)
			CNI	Antimetabolite	Timing of SW			
Late SW vs. steroid maintenance								
Vanrenterghem et al. (19)	446	Yes	TAC	MMF+prednisone	In 2 wk after 3 mo	The same but maintaining steroids	7 (19)	86
Pascual et al. (20)							36 (20)	
Del Castillo et al. (11)	142	Yes	CsA	Myf+prednisone	In 3 mo after 3 mo	The same but maintaining steroids	12	97
Sola et al. (18)	92	No	TAC	MMF+prednisone	In 3 wk after 3 mo	The same but maintaining steroids	24	—
Smak Gregoor et al. (16)	139	Yes	CsA	MMF+prednisone	In 10 wk after 6 mo	The same but maintaining steroids	At least 6	100
Vanrenterghem et al. (17)	500	Yes	CsA	MMF+prednisone	Low-dose prednisone and stopped at 3 mo	The same but maintaining steroids	12	—
Boletis et al. (14)	66	No	CsA	MMF+prednisone	In 6 wk after 6 mo	The same but maintaining steroids	12	86
Pelletier et al. (15)	118	No	CsA	MMF+prednisone	Variable period	The same but maintaining steroids	45	98
Francois et al. (12)	51	No	CsA	MMF+prednisone	After 3 mo	The same but maintaining steroids	36	—
Ahsan et al. (13)	266	Yes	CsA	MMF+prednisone	In 8 wk after 3 mo	The same but maintaining steroids	12	100



CNI Avoidance: Concerns for Nephrotoxicity

Acute

- Dose dependent afferent arteriolar vasoconstriction
- isometric tubular vacuolization
- tubular dysfunction



Chronic

- Associations:
 - Progressive (nodular) arteriolar hyalinosis
 - Glomerular ischemia/sclerosis
 - IFTA
- Mechanisms/existence still debated
 - Increased oxidative stress, fibrogenic cytokines, dysregulated RAAS
 - Low lvl endothelial injury/TMA?

Spare-the-Nephron Trial: MMF + Sirolimus

- Open label, prospective randomized, multicenter study
- KTR on CNI+MMF+/- steroids (n=305)
- Two groups: CNI+MMF vs SRL+MMF (SRL trough 5-10 ng/mL)

	MMF/SRL n=148	MMF/CNI n=151
eGFR at 24 months, ml/min	75.5	71.2
BPAP, %	9.5	11.3
Graft Loss, %	2	4
Death, %	0	3*
Proportion of Patients DC Treatment for AEs,%	21	13



Everolimus vs CsA: The Zeus Study

- Multi-center RCT in KTR 4.5 months post-transplant (n=300)
- IL-2RA + CsA/MPA/steroids randomized to 2 groups
 - Group A: Everolimus (6-10 ng/mL) to M12 + MPA 1440 mg/d + steroids
 - Group B: CsA 125-175 ng/mL to M6, 100-150 ng/mL to M12 +MPA 1440 mg/d + steroids
- Higher rates of proteinuria, stomatitis, HLD treatment and discontinuation rate in Group A

Treatment Arm	Long-term extension: Outcome at 5 Years	
	Adjusted eGFR	BPAR: Cumulative Incidence
Everolimus	66.2 mL/min/1.73 m ²	13.6%
Cyclosporine	60.9 mL/min/1.73 m ²	7.5%



CNI Avoidance: mTOR Inhibitor Studies

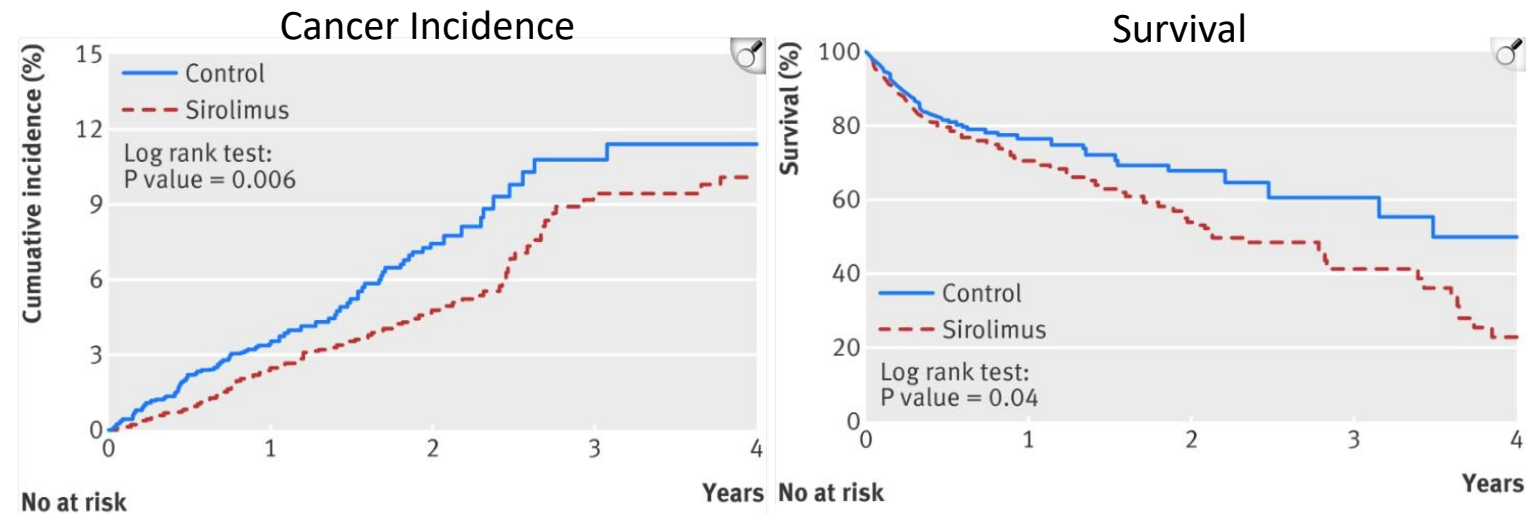
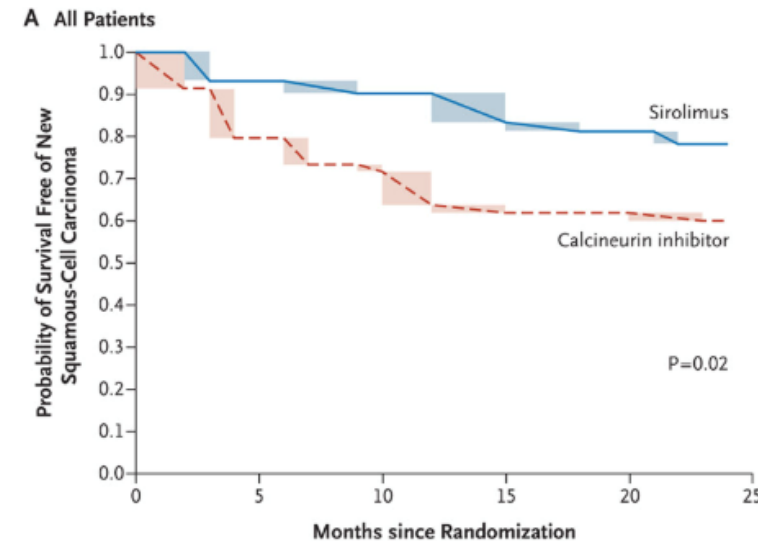
Study	Time to conversion (mo)	Follow-up (mo)	Baseline CNI	GFR (mL/min)	Treatment Failure/Graft Loss	BPAR
CONVERT (SRL)	6-120	12	CsA or TAC	+4.9*	↑	↑
ZEUS (EVR)	4.5	36	CsA	+7.8*	↑	↑
CENTRAL (EVR)	2	12	CsA	+ 8.0*	↑	↑
ORION (SRL)	3	12	TAC	-	↑	↑
SPARE THE NEPHRON (SRL)	1-6	24	80% TAC	+4.6*	- (but 27% back to CNI)	-

*P<0.05; All intent-to-treat



mTORi and cancer

- 64 KTR w/ SCC randomized to SRL vs remaining on CNI¹
- SRL:
 - Fewer new SCC with stable graft function
 - 23% discontinuation rate due to AE
- Meta-analysis from 21 randomized trials (n=5876)²
- SRL:
 - 40% reduction in risk of malignancy (p=0.02)
 - 43% increased risk of death (p<0.001)
 - infection and CVD



¹Euvrard S et al. NEJM 2012; 367:329-39

²Knoll G et al, BMJ. 2014 Nov 24;349:g6679



mTOR Inhibitors: Sirolimus and Everolimus

Dosing:

- TDM (C_0 levels) is employed to maximize the efficacy of both mTORi
- institution-dependent
 - Common Doses
 - Sirolimus: 1 – 2 mg QD
 - Everolimus: 0.75 – 2.25 mg BID

DDI: both agents are substrates for CYP3A4, CYP3A5 and P-gp

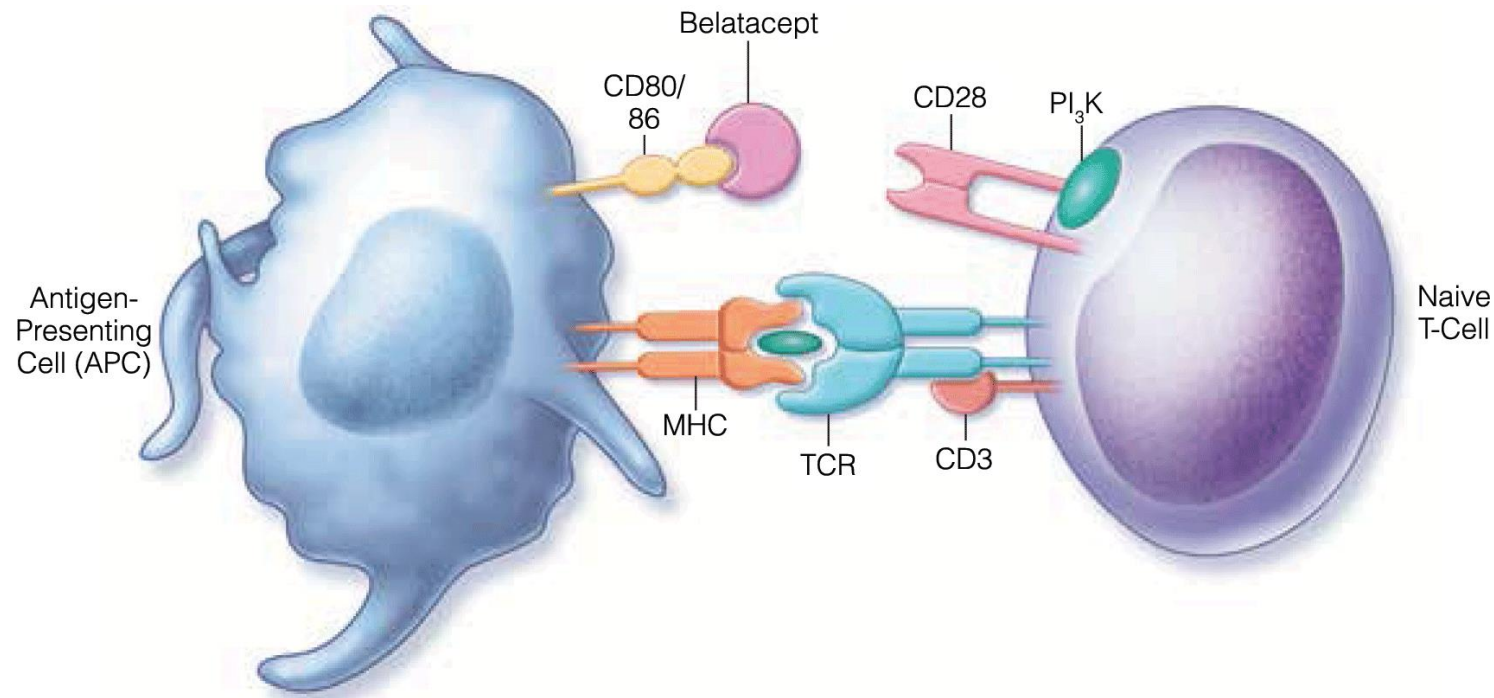
ADR:

- Cardiovascular (hypercholesterolemia, hypertriglyceridemia)
- Myelosuppression
- Dermatologic (rash, mouth ulcers)
- Musculoskeletal (myalgias, muscle weakness)
- Interstitial pneumonitis
- Renal (proteinuria)
 - General precaution not to use in patients with a SCr > 2 mg/dl and/or > 500 mg of proteinuria
- Hepatotoxicity
- Decreased wound healing



Co-Stimulation Blockade: Belatacept

- Fusion protein that acts as a selective T-cell costimulation blocker by binding to CD80/86 receptors on APCs and blocking the required CD28 mediated interaction between APCs and T-cells needed to activate the T-cells.



Co-Stimulation Blockade: Belatacept

Dosing:

- Initial Phase: 10 mg/kg/dose on Days 1 (day of transplant, prior to implantation), and 5, then again at Week 2, 4, 8 and 12.
- Maintenance Phase: 5 mg/kg/dose every 4 weeks (\pm 3 days) beginning at Week 16

DDI: none reported

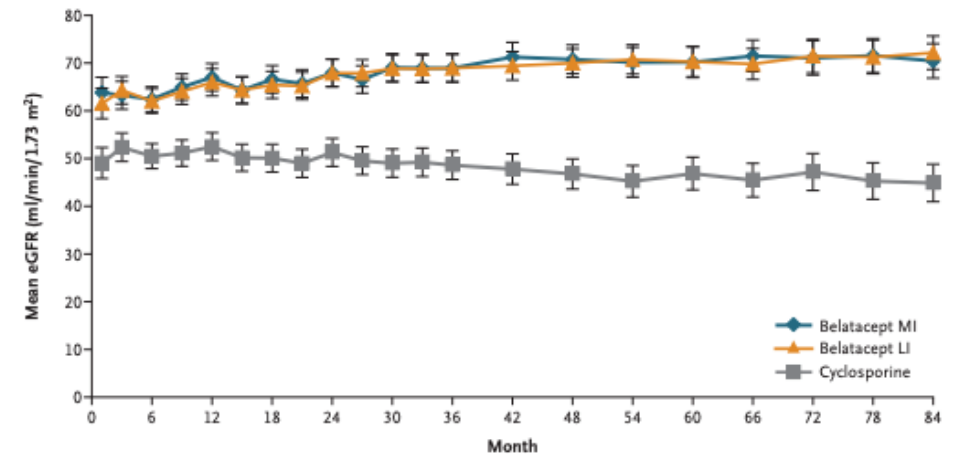
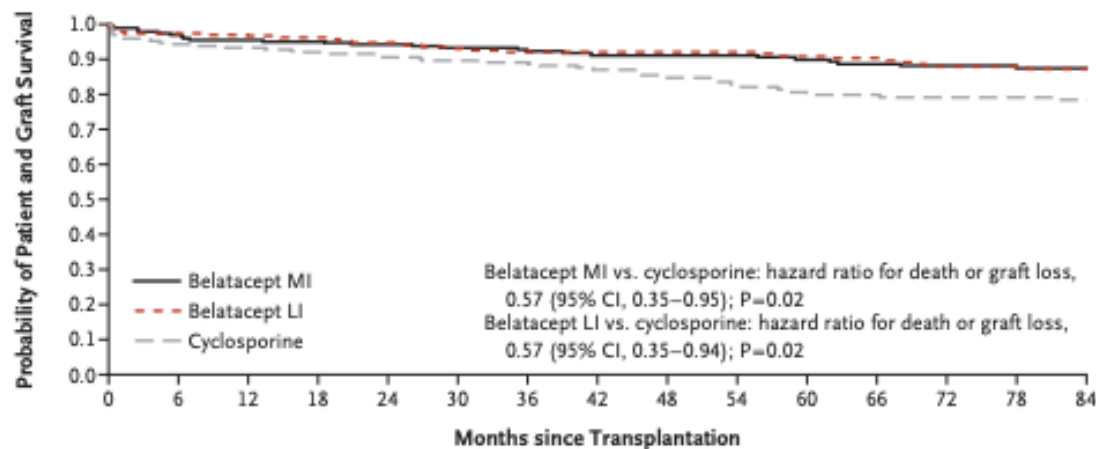
ADR:

- Cardiovascular (edema)
- CNS (fever, HA, insomnia)
- GI (diarrhea, constipation, nausea, abdominal pain)
- GU (UTI)
- Hematologic (myelosuppression)
- Musculoskeletal (arthralgias)
- Respiratory (cough, dyspnea)



BENEFIT and BENEFIT-EXT

- Basiliximab/MMF/pred +:
 - “less intensive” Belatacept
 - “more intensive” Belatacept
 - CsA
- Acute rejection rates higher
- GFR better w/ Bela on 7 yr follow-up ($p < 0.001$)
- Improved patient and graft survival ($p = 0.02$)



Vincenti, Am J Transplant. 2010 Mar;10(3):535-46
 Durrbach, AM J Transplant. 2010
 Vincenti F, NEJM 2016; 374(4):333-43



Belatacept and PTLD

- Pooled data from 3 registration trials reported in FDA Advisory Committee Briefing Document
- EBV (-) recipients have 4-6x higher risk for PTLD than CMS/UNOS registry

	Belatacept MI (n = 477)	Belatacept LI (n = 472)	CsA (n = 476)
PTLD cases	8 (1.7%)	6 (1.3%)	2 (0.4%)
Site of presentation			
Renal	2	3	2
CNS	6	3	0
EBV recipient status			
Negative	5	2	1
Positive	2*	4	0*



Belatacept Conversion

- Prospective, parallel-group, randomized, open-label phase 3b study at 85 centers in ten countries.
- Stable adult kidney transplant recipients 6–60 months post-transplant on CNI
- Two groups: switch to belatacept (n=223) or continue CNI (n=223).
- Higher GFR in Bela group despite higher rates of BPAR
- Similar rates of serious AE, infections, and discontinuations, with no unexpected AE.
 - 1 in bela group w/ PTLD

Table 2. Treatment effect on patient and graft survival (primary end point), BPAR, and renal function at 24 months

End Points	Belatacept Conversion, n=223	CNI Continuation, n=223
Patient and graft survival		
Patients surviving with a functioning graft	219 (98%)	217 (97%)
Adjusted difference from CNI (95.1% CI)	0.8 (−2.1 to 3.7)	
Graft loss or death	4 (2%)	6 (3%)
Graft loss	0	2 (1%)
Death	4 (2%)	4 (2%)
Death with a functioning graft	4 (2%)	4 (2%)
BPAR		
Patients with cellular (Banff 1A or higher) or antibody-mediated BPAR	18 (8%)	9 (4%)
Adjusted difference from CNI (95.1% CI)	4.1 (−0.4 to 8.5)	
All Banff grade (1A or higher) acute cellular rejection events	20 (9%)	6 (3%)
Mild acute (1A)	2 (1%)	4 (2%)
Mild acute (1B)	1 (<1%)	0
Moderate acute (2A)	7 (3%)	1 (<1%)
Moderate acute (2B)	6 (3%)	0
Severe acute (3)	4 (2%)	1 (<1%)
All humoral rejection events	5 (2%)	5 (2%)
Humoral only	0	3 (1%)
Humoral and cellular	5 (2%)	2 (1%)
Renal function		
Mean adjusted eGFR, ml/min per 1.73 m ² (95% CI)		
Month 12	55.0 (53.5 to 56.6)	49.3 (47.7 to 50.8)
Month 18	55.9 (54.3 to 57.6)	48.9 (47.2 to 50.5)
Month 24	55.5 (53.8 to 57.3)	48.5 (46.7 to 50.3)
Mean adjusted change from baseline at month 24 in eGFR, ml/min per 1.73 m ²	+5.2	−1.9
Adjusted difference from CNI (95.1% CI)	7.0 (4.5 to 9.6)	
P value	<0.001	

Data are n (%), unless otherwise stated



TAKE HOME MESSAGES

- Despite some some newer options for induction (i.e., alemtuzumab) and maintenance (i.e., belatacept, everolimus) therapy, there have been little improvement in short- and long-term outcomes in renal transplantation in the past 5-10 years.
- Induction Therapy:
 - Reduction in acute rejection (depleting>non-depleting), though debatable impact on graft survival
- Maintenance Therapy:
 - TAC/MMF +/- steroids remain the primary regimen for most KTRs. Less individualized care due to lack of efficacy or unclear advantages w/ newer agents.
 - Effective immune monitoring tools are needed. Focus of current clinical research is improving long-term outcomes - increasing patient and graft survival and decreasing morbidity.



Question 1

The following best describes the mechanism of action of which immunosuppressant: a chimeric, monoclonal antibody that competitively inhibits the activation of T lymphocytes by blocking the IL-2 receptor.

- A. Basiliximab
- B. Prednisone
- C. Alemtuzumab
- D. Antithymocyte Globulin Rabbit
- E. Tacrolimus



Question 1

The following best describes the mechanism of action of which immunosuppressant: a chimeric, monoclonal antibody that competitively inhibits the activation of T lymphocytes by blocking the IL-2 receptor.

- A. Basiliximab is an IL-2 receptor antagonist and blocks cellular proliferation
- B. Prednisone
- C. Alemtuzumab
- D. Antithymocyte Globulin Rabbit
- E. Tacrolimus



Question 2

Therapeutic drug monitoring (TDM) is commonly used in renal transplant to manage pharmacotherapy. Which of the following immunosuppressants does NOT require TDM.

- A. Tacrolimus
- B. Everolimus
- C. Cyclosporine
- D. Belatacept
- E. Sirolimus



Question 2

Therapeutic drug monitoring (TDM) is commonly used in renal transplant to manage pharmacotherapy. Which of the following immunosuppressants does NOT require TDM.

- A. Tacrolimus
- B. Everolimus
- C. Cyclosporine
- D. Belatacept - the CNI and mTOR inhibitors require TDM. TDM is not necessary when managing a patient receiving belatacept.
- E. Sirolimus



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Halloran PF. Immunosuppressive drugs for kidney transplantation. *New England Journal of Medicine* 2004;351:2715-29.

Gabardi S, Martin S, Roberts K, Grafals M. Induction immunosuppressive strategies in renal transplantation. *American Journal of Health-System Pharmacists* 2011;68:211-8.

Lee RA, Gabardi S. Current trends in immunosuppressive therapies for renal transplant recipients. *American Journal of Health-System Pharmacists* 2012;69:1961-75.

Kim M, Martin ST, Townsend K, Gabardi S. Antibody mediated rejection in kidney transplantation: a review of pathophysiology, diagnosis, and treatment options. *Pharmacotherapy* 2014;34:733-44.



CLINICAL TRIALS

Trial	Change in Management
Brennan DC, et al. <i>N Engl J Med</i> 2006;355:1967-77	<ul style="list-style-type: none"> • rATG becomes primary induction agent due to reduced rates of BPAR compared to IL2RA in high immunologic risk recipients.
Hanaway MJ, et al. <i>N Engl J Med</i> 2011;364:1909-19 (INTAC)	<ul style="list-style-type: none"> • Alemtuzumab shows superiority to IL2RA in low risk KTRs and similar efficacy/safety to rATG in high risk KTRs and becomes a potential option for induction therapy in the US. Of note, regimen was steroid free.
Ekberg et al. <i>NEJM</i> 2007; 357:2562-75 (SYMPHONY)	<ul style="list-style-type: none"> • Tacrolimus demonstrates superiority above CsA (lower AR, improved GS, improved GFR) and becomes primary agent in maintenance IS regimens.
Woodle S et al, <i>Ann Surgery</i> 2008; 248:564-77	<ul style="list-style-type: none"> • Early corticosteroid withdrawal demonstrates similar graft/patient survival and CrCl as steroid maintenance though with higher rates of acute rejection, particularly with IL2RA induction. Majority of centers use triple IS w/ steroid maintenance.
Weir MR et al, <i>Kidney Int.</i> 2011;79(8):897-907	<ul style="list-style-type: none"> • Conversion of CNI to mTORi with only modest benefit in GFR. Other mTORi conversion trials with similar improvement in GFR though with increased rates of AR.
Euvrard S et al. <i>NEJM</i> 2012; 367:329-39	<ul style="list-style-type: none"> • Sirolimus demonstrates reduction in SCC compared to CNI. Later meta-analysis w/ similar reduction in malignancy risk, however higher risk of death (infection, CVD). mTORi may be appropriate in select KTRs with high malignancy risk but should account for other comorbidities.
Vincenti, <i>Am J Transplant.</i> 2010 Mar;10(3):535-46 (BENEFIT)	<ul style="list-style-type: none"> • Belatacept demonstrates improved GFR over CNI despite higher rates of AR.
Budde K, et al. <i>JASN</i> 2021, 32: 3252-64	<ul style="list-style-type: none"> • First multicenter, randomized control study evaluating the impact of conversion to belatacept vs. staying on CNI and demonstrating improvement in eGFR associated with belatacept conversion, despite increased risk of BPAR.