

Maintenance of Immunosuppression Part Two



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Maintenance of Immunosuppression Part Two - Kidney Transplantation

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Disclosures

- Consultant/member of advisory board for Veloxis Pharmaceuticals
- Off-label medication uses will be discussed

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Learning Objectives

- Create an evidence-based maintenance regimen for a kidney transplant recipient that accounts for patient-specific factors.
- Evaluate the role of extended-release tacrolimus formulations and novel immunosuppression regimens.

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Maintenance Immunosuppression Agents

- Calcineurin inhibitors (CNIs)
 - Tacrolimus
 - Immediate-release (IR) tacrolimus capsule (Prograf®)
 - Extended-release (ER) tacrolimus capsule (Astagraf®)
 - Extended-release (XR) tacrolimus tablet (Envarsus®)
 - Cyclosporine
 - Modified cyclosporine (Neoral®, Gengraf®)
 - Non-modified cyclosporine (Sandimmune®)

Lim 2017

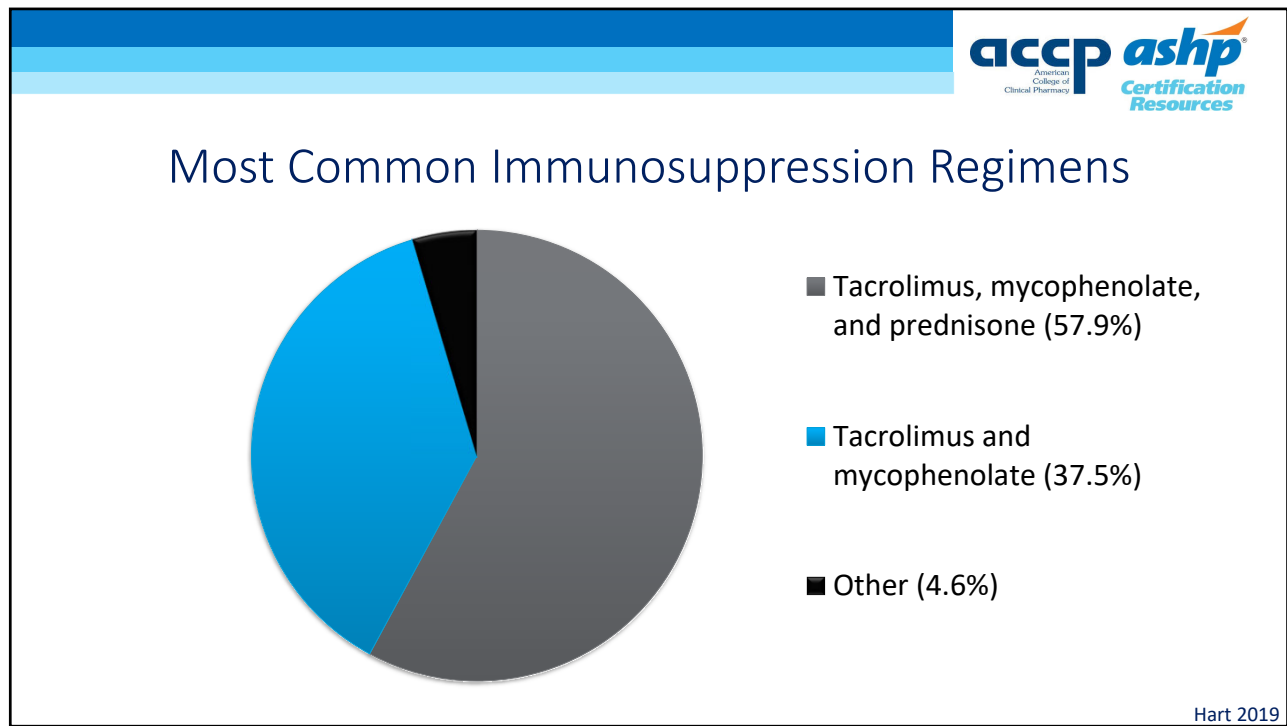
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Maintenance Immunosuppression Agents

- Antimetabolites
 - Mycophenolic acid (Myfortic®)
 - Mycophenolate mofetil (Cellcept®)
 - Azathioprine (Imuran®)
- Corticosteroids
- Belatacept (Nulojix®)
- Mammalian target of rapamycin inhibitors (mTORi)
 - Sirolimus (Rapamune®)
 - Everolimus (Zortress®)

Lim 2017

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Comparison of Tacrolimus and Cyclosporine with Azathioprine

- Long-term comparison of tacrolimus (IR-tac) or cyclosporine (CSA) with azathioprine (AZA) and maintenance prednisone in a low immunological risk population
- Open-label prospective, randomized, multicenter trial
 - Induction with muromonab-CD3 (OKT3) or horse antithymocyte globulin (Atgam)
 - Group 1: CSA, AZA, and prednisone (n=207)
 - Group 2: IR-tac, AZA, and prednisone (n=205)

Pirsch 1997;Vincenti 2002

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Comparison of Tacrolimus and Cyclosporine with Azathioprine

- No difference observed in patient survival at 1 or 5 years
- Increased rate of acute cellular rejection (ACR) in CSA group
 - 46.4% in CSA group versus 30.7% IR-tac group (p=0.11)
- More patients in CSA group with severe rejection (p=0.001) and requirement of lymphocyte depleting agent for treatment of rejection (p<0.001)
- At 5 years, 27% of patients in CSA group were converted to IR-tac and 9.3% of patients in IR-tac arm were converted to CSA
 - Majority of crossover patients from CSA to IR-tac due to ACR

Pirsch 1997;Vincenti 2002

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Comparison of Tacrolimus and Cyclosporine with Mycophenolate

- Long-term comparison of IR-tac and mycophenolate mofetil (MMF) or AZA versus CSA and MMF with maintenance corticosteroids in a low immunological risk population
- 3 year prospective, randomized, multicenter trial
 - Antibody induction only in patients with delayed graft function (DGF)
 - Group 1: IR-tac, MMF, and prednisone (n=72)
 - Group 2: CSA, MMF, and prednisone (n=75)
 - Group 3: IR-tac, AZA and prednisone (n=76)

Gonwa 2003

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Comparison of Tacrolimus and Cyclosporine with Mycophenolate

- No difference in overall patient or graft survival at 3 years
 - Group 1 had increased graft survival in patients with DGF (p=0.02)
- Numerically lower number of ACR in group 1 but not statistically significant
- African American patients in group 1 had decreased incidence of ACR and severity but not statistically significant
- More patients in CSA groups converted to IR-tac due to ACR

Gonwa 2003

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Tacrolimus versus Cyclosporine: Key Differences in Adverse Effects

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|--|---|
| <ul style="list-style-type: none"> • Tacrolimus <ul style="list-style-type: none"> – Neurotoxicity – New onset diabetes after transplant (NODAT) – Alopecia | <ul style="list-style-type: none"> • Cyclosporine <ul style="list-style-type: none"> – Hypertension – Hyperlipidemia – Hirsutism – Gingival hyperplasia |
|--|---|

Pirsch 1997;Vincenti 2002;Gonwa 2003

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Tacrolimus versus Cyclosporine: Key Points

- Original studies
 - No overall differences in patient or graft survival
 - Decreased severity of rejection and need for lymphocyte depleting agent for treatment of rejection with tacrolimus
 - Increased risk of post-transplant diabetes with tacrolimus
 - Increased risk of hypertension and hyperlipidemia with cyclosporine
- KDIGO guidelines suggest use of tacrolimus over cyclosporine as initial CNI
- Larger meta-analyses show reduced risk of graft loss, patient mortality, acute rejection, and steroid resistant rejection with tacrolimus

Pirsch 1997;Vincenti 2002;Gonwa 2003;Webster 2005;KDIGO 2009;Liu 2016

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Tricontinental Mycophenolate Mofetil Study

- Prospective, double-blind, multicenter trial to compare MMF and AZA with standard immunosuppression regimens in kidney transplant recipients without induction
 - Group 1: CSA, MMF 3 grams daily, and prednisone (n=164)
 - Group 2: CSA, MMF 2 grams daily, and prednisone (n=173)
 - Group 3: CSA, weight-based AZA, and prednisone (n=166)

Tricontinental renal study group 1996

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Tricontinental Mycophenolate Mofetil Study

- Treatment failure (biopsy proven acute rejection (BPAR), graft loss, patient death, or discontinuation of study drug) at 6 months
 - 34.8% in group 1; 38.3% in group 2; 50% in group 3
- BPAR at 6 months
 - 15.9% in group 1; 19.7% in group 2; 35.5% in group 3
- Less patients in group 1 required lymphocyte depleting therapy for treatment of rejection
- More patients in MMF groups experienced leukopenia and gastrointestinal (GI) side effects

Tricontinental renal study group 1996

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Mycophenolate in African American Patients

- Post-hoc analysis of MMF versus AZA in African American kidney transplant recipients from U.S Mycophenolate Mofetil Study Group
 - Similar treatment groups as Tricontinental study but all patients received induction with thymoglobulin
- Primary endpoint was composite biopsy proven rejection or treatment failure defined as graft loss, death, or withdrawal from the study
 - Primary endpoint in African American patients was lowest in MMF 3 grams daily group
 - African American patients in MMF 3 grams daily group required less treatment for rejection

Sollinger 1995; Neylan 1997

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Mycophenolic Acid (Myfortic®) versus Mycophenolate Mofetil (Cellcept®)

- In combination with CSA and maintenance corticosteroids (n=423)
 - No difference in efficacy failure (BPAR, graft loss, death, loss to follow-up) at 6 and 12 months
 - Similar rates of GI side effects and dose reductions for GI side effects
- In combination with tacrolimus and early steroid withdrawal (n=150)
 - No difference in rates of rejection, renal function, patient or graft survival up to 4 years post-transplant
 - No differences in rates of upper or lower GI side effects

Salvador 2004; Ciancio 2008, Ciancio 2011

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Corticosteroid Withdrawal (CSWD)

- CSWD at 90 days post-transplant in recipients on CSA and MMF (n=266)
 - Rejection or treatment failure higher in CSWD arm (30.8% versus 9.8%; $p=0.0007$) and increased risk in African American recipients (39.6% versus 16%; $p<0.001$)
 - No difference in patient or graft survival
- Early corticosteroid withdrawal (CSWD) at 7 days versus chronic corticosteroid (CCS) use with basiliximab or thymoglobulin induction, tacrolimus, and MMF (n=386)
 - No difference in composite primary endpoint of death, graft loss, moderate/severe rejection, or rejection requiring lymphocyte depleting therapy at 5 years
 - Increased BPAR with CSWD using Kaplan Meier analysis ($p=0.04$)
 - CCS more likely to require lymphocyte depleting therapy for treatment of rejection ($p=0.01$)
 - In CSWD subgroup analysis, 14.4% BPAR with thymoglobulin induction versus 24.2% with basiliximab induction ($p=0.09$)
 - African American patients did not experience increased rates of BPAR with CSWD

Ashan 1999;Woodle 2008

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Balancing Pros and Cons of Corticosteroids

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|---|---|
| <ul style="list-style-type: none"> • Corticosteroid withdrawal <ul style="list-style-type: none"> – Increase in rates of rejection – No difference in overall graft or patient survival – Avoid long-term side effects of steroids | <ul style="list-style-type: none"> • Corticosteroid Maintenance <ul style="list-style-type: none"> – Decreased incidence of rejection – Increased risk of long-term side effects of corticosteroids |
|---|---|

Ashan 1999;Woodle 2008;Knight 2010;Nikkel 2012;Haller 2016

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Active Learning Case 1

A 39-year-old African American woman with end-stage renal disease due to polycystic kidney disease is admitted for deceased donor kidney transplant. Peak class I and II PRA are 0%, T and B cell crossmatch is negative, and recipient does not have any historical or current donor specific antibody (DSA). Patient will receive induction with thymoglobulin per center protocol for high immunological risk due to race. What is the optimal maintenance immunosuppression to reduce risk of rejection in this patient?

- A. Cyclosporine and azathioprine
- B. Cyclosporine and mycophenolate
- C. Tacrolimus and azathioprine
- D. Tacrolimus and mycophenolate

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Alternative and Novel Maintenance Immunosuppression

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Comparison of Tacrolimus Formulations (ASTCOFF)

- Open-label, randomized, 2-sequence, 3-period crossover study that evaluated the pharmacokinetic (PK) profiles of IR-tac, tacrolimus ER (ER-tac), and tacrolimus XR (LCPT) in kidney transplant recipients on stable IR-tac doses
 - Utilized conversion rates of 1:1:0.8
- PK profile comparison
 - IR-tac and ER-tac have similar PK profiles
 - When normalized to IR-tac, LCPT had decreased peak levels and less trough to peak fluctuation
- Recommended conversion rates from based on normalized exposure
 - IR-tac to LCPT -30%
 - IR-tac to ER-tac +8%
 - ER-tac to LCPT -36%

Tremblay 2017

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LCPT in African American Patients (ASERTAA)

- Open-label, prospective, randomized, 2-sequence, 3-period, crossover study to compare PK of IR-tac versus LCPT in stable African American kidney transplant recipients
- Increased total daily dose for IR-tac and LCPT in CYP3A5 expressers
- IR-tac in CYP3A5 expressers versus nonexpressers
 - No difference in overall exposure or trough levels
 - 33% increased peak in CYP3A5 expressers (p=0.04)
- LCPT in CYP3A5 expressers versus nonexpressers
 - No difference in overall exposure, trough, or peak levels
- When converting from IR-tac to LCPT, a total daily reduction of 20% will achieve equivalent exposure

Trofe-Clark 2018

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Benefit of LCPT in Patients with Tremor (STRATO)

- 2-sequence, open-label, prospective, phase 2b, multicenter study that assessed conversion of IR-tac to LCPT in stable kidney transplant recipients with tremors
- Primary endpoint was mean change from baseline in the total Fahn-Tolosa-Marin (FTM) score after 7 days
 - Improvement of FTM score was -5.35 from baseline ($p < 0.0001$)
 - Statistically significant improvement in tremor using mean and percent change in Fahn-Tolosa-Marin (FTM) after 7 days
- Statistically significant improvement in reported quality of life

Langone 2015

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LCPT Pooled Analysis

- Pooled analysis of 2 two arm, parallel-group, prospective, randomized, multicenter clinical trials comparing IR-tac and LCPT
 - Conversion in stable kidney transplant recipients (38%) and de novo kidney transplant recipients (62%)
- Primary endpoint was composite endpoint of treatment failure
 - Death, graft failure, biopsy-proven acute rejection, or lost to follow-up
 - Stratified by sex, age, and race
- LCPT had fewer treatment failures in African American recipients and recipients ≥ 65 years old

Bunnapradist 2016

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Long-Term Outcomes of Belatacept (BENEFIT)

- Randomized, active-controlled, parallel group, multicenter trial in a low immunological risk population
 - Group 1: basiliximab, more intensive (MI) belatacept, mycophenolate, and prednisone
 - Group 2: basiliximab, less intensive (LI) belatacept, mycophenolate, and prednisone
 - Group 2: basiliximab, CSA, mycophenolate, and prednisone
- Primary endpoint was composite patient and graft survival, renal function, and acute rejection at 1 year
 - No difference in patient or graft survival at 1 year
 - eGFR improved in both belatacept groups compared to CSA at 1 year
 - Higher incidence of rejection in both belatacept groups at 1 year

Vincenti 2010

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Long-Term Outcomes of Belatacept (BENEFIT)

- Long-term data at 7 years continue to show benefit of belatacept
 - eGFR at 7 years improved in both belatacept groups
 - 70.4 mL/min in MI belatacept group ($p < 0.0001$ compared to CSA)
 - 72.1 mL/min in LI belatacept group ($p < 0.0001$ compared to CSA)
 - 44.9 mL/min in CSA group
 - Decreased formation of DSA in both belatacept groups at 7 years
 - 43% reduction in the risk of graft loss or death with belatacept

Vincenti 2016

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Belatacept with Early Steroid Withdrawal (BEST)

- Prospective, randomized, open-label, multicenter study in a low immunologic risk patient population with more modern immunosuppression regimen
 - Group 1: alemtuzumab, belatacept, mycophenolate, and early steroid withdrawal (ESW)
 - Group 2: rabbit antithymocyte globulin (rATG), belatacept, mycophenolate, and ESW
 - Group 3: rATG, tacrolimus, mycophenolate, and ESW
- No difference in primary endpoint of composite rate of patient death, allograft loss, or eGFR less than 45 mL/min at 12 months
 - ESW with belatacept and lymphocyte depletion induction was not superior to tacrolimus for composite endpoint

Woodle 2019

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Belatacept with Early Steroid Withdrawal (BEST)

- Increased BPAR and requirement of rATG for treatment of rejection in belatacept groups
 - Rejection was 15.9% in group 1; 22.1% in group 2; 4.8% in group 3
 - Use of rATG for rejection was 6.5% in group 1; 13.5% in group 2; 0% in group 3
 - Use of maintenance corticosteroids at 1 year was 18.7% in group 1; 14.4% in group 2; 8.6% in group 3
- No differences in renal function between groups at 1 year
- No difference in DSA between groups at 1 year
- Trend in reduction of NODAT favored belatacept groups

Woodle 2019

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De Novo Belatacept with Prolonged Tacrolimus Taper

- Comparison of evolving de novo belatacept regimens versus standard of care with tacrolimus in diverse patient population
 - All patients received basiliximab induction, MMF, and maintenance corticosteroids
- High rates of early rejection in belatacept groups without tacrolimus taper
- Improved rates of early rejection when tacrolimus tapered off by 5 months post-transplant
 - High rates of rejection after tacrolimus discontinued
- Comparable rates of rejection to standard of care when tacrolimus taper extended to 11 months
- eGFR in all belatacept groups was 63.8 mL/min versus 46.2 mL/min in tacrolimus group ($p < 0.0001$)
- No differences in patient or graft survival

Adams 2017

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Belatacept Conversion

- Rostaing, et al (2011)
 - Evaluate safety and efficacy of conversion to belatacept in stable kidney transplant recipients that were 6 to 36 months post-transplant (n=84)
 - Belatacept 5 mg/kg on days 1, 15, 29, 43, 57 and then every 28 days thereafter
 - CNIs 100% of dose on days 1 to 14, 40 to 60% of dose on days 15 to 22, 20 to 30% of dose on days 23 to 28, and discontinued on day 29
 - 89% of patients on in belatacept arm received maintenance corticosteroids
 - Mean eGFR was 60.5 mL/min in belatacept group versus 56.5 mL/min in CNIs group ($p = 0.0058$)
 - 7% rejection within 1-year post-transplant in belatacept group versus no rejection episodes in CNIs group
 - No differences in patient or graft survival

Rostaing 2011

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Belatacept Conversion

- Wojciechowski, et al (2017)
 - 20 patients within 90 days of transplant were converted to belatacept for prolonged DGF
 - Belatacept 10 mg/kg on day 0, 14, 28, then 5 mg/kg on day 42, 56, and monthly thereafter
 - Tacrolimus goal 8 to 12 ng/mL through days 0 to 13 of conversion then tacrolimus dose decreased by 50% on days 14 to 27 then discontinued on day 28
 - All patients were maintained on corticosteroids
 - Mean eGFR increased from 16 mL/min to 43.1 mL/min 30 days after conversion ($p < 0.0001$) and improvement in renal function was significantly better in patients converted earlier (< 30 days) after transplant
 - 20% rejection in patients converted to belatacept
 - No difference in patient or graft survival
- Cohorts have shown conversion to belatacept as an acceptable alternative to CNIs in high immunologic risk recipients and patients with mild DSA

Gupta 2015;Wojciechowski 2017;Ulloa 2019

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Use of mTORi in Kidney Transplant

- Not commonly used de novo
 - Intolerance due to rejection and side effect profile
 - Concern for decreased wound healing
 - Most studies don't reach goal trough levels
- Potential for anti-viral benefit
 - Increase efficacy of memory T cells in response to viral stimuli
 - Inhibit viral cell growth and viral protein synthesis
 - Potential benefit in reducing risk of CMV or BK infection
- Potential for anti-tumor benefit
 - Post-transplant malignancy

Ekberg 2007;Klintman 2014;Tedesco-Silva 2015;Bhat 2015;Bowman 2018;Berger 2019

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Reduced Exposure to CNI (Symphony)

- Prospective, randomized, open-label, multicenter study in low immunological risk kidney transplant recipients
 - Group 1: daclizumab, standard dose cyclosporine (STD CSA) goal trough 100 to 300 ng/mL, MMF, and prednisone (n=390)
 - Group 2: daclizumab, low dose cyclosporine (LOW CSA) goal trough 50-100 ng/mL, MMF, and prednisone (n=399)
 - Group 3: daclizumab, low dose tacrolimus (FK) goal trough 3-7 ng/mL, MMF and prednisone (n=401)
 - Group 4: daclizumab, low dose sirolimus (SRL) goal trough 4-8 ng/mL, MMF, and prednisone (n=399)

Ekberg 2007

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Reduced Exposure to CNI (Symphony)

- Primary end point was eGFR at 12 months
 - eGFR was highest in FK group (65.4 mL/min in FK versus 57 to 59 mL/min in other groups, $p < 0.001$)
- Secondary endpoints included rejection and patient and graft survival
 - Lowest incidence of rejection in FK group and highest incidence of rejection in SRL group at 6 and 12 months
 - Six month: 11.3% versus 35.3% ($p < 0.001$)
 - Twelve month: 12.3% versus 37.2% ($p < 0.001$)
 - No statically significant difference in allograft or patient survival
- More serious safety events reported in SRL group
 - 53.2% in SRL versus 43% to 44% in other groups
 - More patients in SRL group discontinued due to adverse events
 - More treatment failure with sirolimus

Ekberg 2007

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Active Learning Case 2

A 70-year-old man received a living donor kidney transplant 1 month ago. His immunosuppression regimen consists of tacrolimus 5 mg 2 times daily with trough levels ranging 7-9 ng/mL for the past two weeks and mycophenolic acid 720 mg 2 times daily. He reports his tremor continues to worsen and is affecting his ability to eat, write, and put on clothes. The PharmD sees him in clinic and recommends conversion to tacrolimus XR due to impact of tremor on quality of life. What dose of tacrolimus XR do you recommend?

- A. Tacrolimus XR 6.5 mg daily
- B. Tacrolimus XR 7 mg daily
- C. Tacrolimus XR 8 mg daily
- D. Tacrolimus XR 10.75 mg daily

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Key Takeaways

- Most centers use tacrolimus and mycophenolate-based regimens in kidney transplant recipients
 - 57.9% of centers continue to use maintenance corticosteroids
- Use of LCPT decreases peak concentration levels and toxicity associated with high peak levels
 - Benefit of LCPT has been established in patients with tremor and patients who are rapid metabolizers of tacrolimus
- Further studies needed to establish long-term benefit of belatacept with modern immunosuppression regimens and mTORi-based regimens as alternative immunosuppression regimens

Hart 2019

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Maintenance Immunosuppression Part Two - Liver Transplantation

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Disclosures

- I serve as a consultant for Wolters-Kluwer
- I will be discussing off-label medication use

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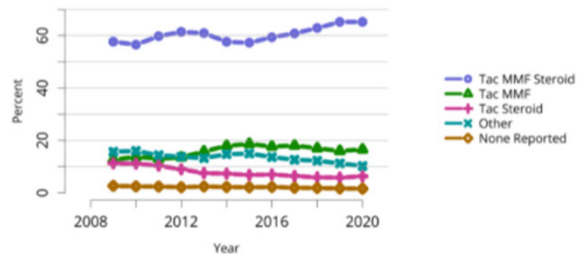
Learning Objectives

- Evaluate maintenance immunosuppression regimens for liver transplant recipients that account for patient-specific factors.
- Design evidence based maintenance immunosuppression regimens for liver transplant recipients.

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Trends in Maintenance Immunosuppression

OPTN/SRTR 2020 Annual Data Report



- Approximately 60% of liver transplant (LT) recipients are initiated on a triple drug regimen
 - Tacrolimus (TAC), mycophenolate (MMF), and steroids
- Dual maintenance regimens are less common
 - TAC and MMF (less than 20%)
 - TAC and Steroid (less than 10%)

https://srtr.transplant.hrsa.gov/annual_reports/2020/Liver.aspx. Accessed April 2022.

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Role of Calcineurin Inhibitors (CNIs)

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Comparison of Calcineurin Inhibitors (CNI) in LT

Design	<ul style="list-style-type: none"> Randomized, comparative, open-label study Study time period: August 1990 to October 1996
Population	<ul style="list-style-type: none"> Primary liver transplant recipients (n=529) Performed at twelve centers in the United States
Intervention	<ul style="list-style-type: none"> Comparison of TAC to cyclosporine (CYA) based immunosuppression regimens <ul style="list-style-type: none"> Patients initially received intravenous CNI formulations Transitioned to oral formulation when clinically appropriate

Wiesner RH. Transplantation 1998;66(4):493-499.

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Comparison of CNIs in LT

	Tacrolimus (n=263)	Cyclosporine (n=266)
Dosing	<ul style="list-style-type: none"> Intravenous: <ul style="list-style-type: none"> Initially 0.075 mg/kg IV BID Reduced to 0.05 mg/kg IV BID due to reports of renal impairment Transition to oral: 0.15 mg/kg PO BID 	<ul style="list-style-type: none"> Varied among centers 1 mg/kg IV Q12H (10 centers) Transition to oral administration when clinically appropriate
Dosing adjustments	<ul style="list-style-type: none"> Trough concentrations, toxicities, and rejection 	<ul style="list-style-type: none"> Target trough levels between 250-400 ng/mL
Concomitant medications	<ul style="list-style-type: none"> Hydrocortisone 1000 mg IV at surgery Followed by methylprednisolone taper, then oral prednisone 20 mg/day 	<ul style="list-style-type: none"> Steroids began intraoperatively Azathioprine used at the majority of centers Antithymocyte globulin (one center)

Wiesner RH. Transplantation 1998;66(4):493-499.

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Results: Comparison of CNIs in LT

- Similar survival rates at 5 years post-transplant between treatment groups
 - Patient survival: 79% in TAC vs 73.1% in CYA (p=0.15)
 - Graft survival: 71.8% in TAC vs 66.4% in CYA (p=0.21)
- Lower incidence of biopsy confirmed rejection during the first year post transplant in the TAC group (68%) vs CYA group (76%)
- Comparable safety profiles between treatment groups

Wiesner RH. Transplantation 1998;66(4):493-499.

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Delayed CNI Initiation

	Yoshida, et al	Calmus, et al	Neuberger, et al
Design	Randomized, multicenter study	Randomized, open-label, comparative multicenter trial	Prospective, randomized, open-label, parallel group multicenter study
Population	<i>De novo</i> adult liver transplant recipients (n=148)	<i>De novo</i> adult liver transplant recipients (n=199)	<i>De novo</i> liver transplant recipients > 16 years of age (n=517)
Intervention	<ul style="list-style-type: none"> • <u>Control arm (n=76)</u>: standard TAC, MMF + steroid taper • <u>Study arm (n=72)</u>: daclizumab, delayed low-dose TAC (POD#4-6), MMF + steroid taper 	<ul style="list-style-type: none"> • <u>Control arm (n=101)</u>: standard TAC (day 0), MMF + steroids • <u>Study arm (n=98)</u>: Daclizumab, delayed TAC (POD#5), MMF + steroids 	<ul style="list-style-type: none"> • <u>Group A (n=181)</u>: standard TAC + steroids • <u>Group B (n=168)</u>: reduced TAC, MMF + steroids • <u>Group C (n=168)</u>: delayed, reduced TAC (POD#5), MMF + steroids, daclizumab

Yoshida EM, Marotta PJ, Greig PD, et al. Liver Transpl 2005;11(9):1064-1072. Calmus Y, Kamar N, Gugenheim J, et al. Transplantation 2010;89(12):1504-1510. Neuberger JM, Mamelok RD, Neuhaus P, et al. Am J Transplant 2009;9(2):327-336.

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Conclusions: Delayed CNI Initiation

	Yoshida, et al	Calmus, et al	Neuberger, et al
TAC trough goals (ng/mL)	Control arm: 10 for 30 days Study arm: 4-8	Both arms: 10-20 x first 4 weeks	Group A: >10 x first month Group B&C: ≤8 entire study
Results	<ul style="list-style-type: none"> No statistically significant difference in acute rejection ($p=0.68$) or patient survival ($p=0.21$) Statistically significant differences in median GFR favoring investigational arm seen at 6 months post-transplant 	<ul style="list-style-type: none"> No significant difference in SCr level more than 130 $\mu\text{mol/L}$ (1.47 mg/dL) at any time point evaluated BPAR was similar between groups at 6, 12, and 24 months Patient and graft survival was comparable 	<ul style="list-style-type: none"> eGFR decreased by 23.61, 21.22, and 13.63 mL/min in groups A, B, and C, respectively (A vs C, $p=0.012$; A vs B, $p=0.199$) BPAR rates not statistically significant between the groups Patient and graft survival were comparable

Yoshida EM, Marotta PJ, Greig PD, et al. Liver Transpl 2005;11(9):1064-1072. Calmus Y, Kamar N, Gugenheim J, et al. Transplantation 2010;89(12):1504-1510. Neuberger JM, Mamelok RD, Neuhaus P, et al. Am J Transplant 2009;9(2):327-336.

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CNI Minimization Strategies

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MMF with Reduced CNI

	Beckebaum, et al	Boudjema, et al	Pageaux, et al
Design	Prospective, randomized single center study	Prospective, controlled, randomized, nonblinded, two-parallel group study	Prospective, randomized, multicenter study
Population	Adult LT \geq 1 year post-transplant and SCr $>$ 1.2 mg/dL	Adults receiving first deceased donor LT; <i>de novo</i> reduced TAC	LT recipients $>$ 1 year post-transplant with CNI-related renal impairment
Intervention	<ul style="list-style-type: none"> Standard CNI dose (n=30) MMF plus CNI reduction (n=60) 	<ul style="list-style-type: none"> Full dose TAC (control) (n=100) MMF plus reduced dose TAC (n=95) 	<ul style="list-style-type: none"> No MMF, but ability to reduce CNI (n=29) MMF plus reduced dose CNI (n=27)

Beckebaum S, Klein CG, Sotiropoulos GC, et al. Transplant Proc 2009;41(6):2567-2569. Boudjema K, Camus C, Saliba F, et al. Am J Transplant 2011;11(5):965-976. Pageaux GP, Rostaing L, Calmus Y, et al. Liver Transpl 2006;12(12):1755-1760.

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Conclusions: MMF with Reduced CNI

	Beckebaum, et al	Boudjema, et al	Pageaux, et al
CNI trough goals (ng/mL)	Standard group: not defined Study group: 2-4 ng/mL (TAC) and 25-50 ng/mL (CYA)	Control group: \geq 12 ng/mL for 6 weeks then decrease goal Study group: \leq 10 ng/mL for 6 weeks then decrease goal	Not defined in either group Study group: targeted 50% CNI dose reduction
Results	<ul style="list-style-type: none"> At 12 months, statistically significant improvement in SCr and eGFR in the MMF group Similar patient and graft survival rates 	<ul style="list-style-type: none"> Statistically significant reduction in renal dysfunction in the study group Reduction in acute cellular rejection (ACR) in the study group 	<ul style="list-style-type: none"> Study group: significant decrease in SCr and increase in CrCl at 12 months No rejection episodes in study group

Beckebaum S, Klein CG, Sotiropoulos GC, et al. Transplant Proc 2009;41(6):2567-2569.
 Boudjema K, Camus C, Saliba F, et al. Am J Transplant 2011;11(5):965-976.
 Pageaux GP, Rostaing L, Calmus Y, et al. Liver Transpl 2006;12(12):1755-1760.

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mTOR Inhibitor with Reduced CNI

	Saliba, et al	Asrani, et al
Design	Prospective, randomized, open-label, multicenter study	Randomized, open-label, active controlled, parallel group multicenter study
Population	<i>De novo</i> LT patients (n=719)	<i>De novo</i> adult deceased donor LT recipients (n=222)
Intervention	3 treatment arms <ul style="list-style-type: none"> • Everolimus (EVR) + reduced TAC • TAC control • TAC elimination 	2 treatment arms <ul style="list-style-type: none"> • Conventional dose TAC + steroids • Sirolimus (SRL) + reduced dose TAC + steroids

Saliba F, De Simone P, Nevens F, et al. Am J Transplant 2013;13(7):1734-1745.

Asrani SK, Wiesner RH, Trotter JF, et al. Am J Transplant 2014;14(2):356-366.

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Conclusions: mTOR Inhibitor with Reduced CNI

	Saliba, et al	Asrani, et al
Results	<ul style="list-style-type: none"> • TAC elimination arm stopped early due to ↑ rates of tBPAR • Comparable rate of tBPAR, graft loss, & death at 24 months between remaining treatment arms • Adjusted change in eGFR and mean eGFR at 24 months was superior in the EVR+reduced TAC arm 	<ul style="list-style-type: none"> • Terminated early due to imbalance of HAT/PVT events in SRL treatment arm <ul style="list-style-type: none"> • Results from this study led to Black Box Warning • Higher cumulative incidence of graft loss, patient death, and sepsis at 24 months in SRL group

Saliba F, De Simone P, Nevens F, et al. Am J Transplant 2013;13(7):1734-1745.

Asrani SK, Wiesner RH, Trotter JF, et al. Am J Transplant 2014;14(2):356-366.

Fischer L, Saliba F, Kaiser GM, et al. Transplantation 2015;99(7):1455-1462.

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Conversion from CNI to mTOR inhibitor



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Conversion from CNI to SRL



	Abdelmalek, et al	Teperman, et al
Design	Prospective, randomized, open-label, parallel group study	Prospective, open-label, multicenter study
Population	Patients ≥ 13 years of age who were 6 months to 12 years post-LT (n=607)	Recipients of first LT (n=293)
Intervention	Two treatment arms <ul style="list-style-type: none"> • CNI continuation (n=214) • SRL conversion (n=393) Antimetabolites & steroids allowed	Two treatment arms <ul style="list-style-type: none"> • MMF + SRL (n=148) • MMF + CNI (n=145)

Sirolimus Black Box Warnings in *de novo* liver transplant recipients:

- Use in combination with tacrolimus associated with excess mortality and graft loss
- Use in combination with cyclosporine or tacrolimus associated with an increase in HAT

Abdelmalek MF, Humar A, Stickel F, et al. Am J Transplant 2012;12(3):694-705.

Teperman L, Moonka D, Sebastian A, et al. Liver Transpl 2013;19(7):675-689.

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Conclusions: Conversion from CNI to SRL

	Abdelmalek, et al	Teperman, et al
Results	<ul style="list-style-type: none"> Changes in baseline renal function at month 12 was not significant between the treatment groups Higher rates of BPAR ($p=0.02$) and discontinuation ($p<0.001$) in the SRL conversion arm No significant benefit identified between groups at 1 year after conversion 	<ul style="list-style-type: none"> Statistically significant improvement in renal function from baseline in MMF/SRL compared to MMF/CNI ($p=0.0012$) Incidence of BPAR was significantly greater in MMF/SRL arm Graft loss and death were similar Higher percentage of study withdrawal due to ADEs in the MMF/SRL arm

Abdelmalek MF, Humar A, Stickel F, et al. Am J Transplant 2012;12(3):694-705.

Teperman L, Moonka D, Sebastian A, et al. Liver Transpl 2013;19(7):675-689.

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Conversion from CNI to EVR

	PROTECT Study
Design	Prospective, randomized, open-label, parallel group study
Population	De novo LT recipients between 18-70 years of age (n=203)
Intervention	Two treatment arms: CNI continuation (n=102) and EVR conversion (n=101)
Results	<p>One-year outcomes (n=177 completed core study):</p> <ul style="list-style-type: none"> No significant difference in mean cGFR between groups using CrCl <p>Three-year outcomes (n=60 completed extension study):</p> <ul style="list-style-type: none"> Small difference in adjusted mean eGFR favoring CNI-free regimen <p>Five-year outcomes: (n=53)</p> <ul style="list-style-type: none"> Adjusted mean eGFR was significantly higher in EVR group using CrCl ($p=0.031$) Comparable patient and graft outcomes

Fischer L, Klempnauer J, Beckebaum S, et al. Am J Transplant 2012;12(7):1855-1865.

Sterneck M, Kaiser GM, Heyne N, et al. Am J Transplant 2014;14(3):701-710.

Sterneck M, Kaiser GM, Heyne N, et al. Clin Transplant 2016;30(6):741-748.

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Conversion from TAC to EVR

Design	<ul style="list-style-type: none"> Randomized, open-label multicenter study
Population	<ul style="list-style-type: none"> De novo LT recipients (n=188) Performed at 15 centers in France from 2012 to 2015
Intervention	Randomized at 4 weeks post-transplant <ul style="list-style-type: none"> TAC-based therapy (n=95) EVR with low exposure TAC discontinued by month 4 (n=93) Both groups received basiliximab, enteric coated mycophenolic sodium with or without steroids
Results	<ul style="list-style-type: none"> Change in eGFR using MDRD was superior in EVR group at 24 weeks ($p<0.001$) Mean eGFR at week 24 was higher in EVR group ($p<0.001$) Treated BPAR, graft loss, and death were similar between groups More EVR patients (17.8%) discontinued therapy due to adverse events compared to TAC patients (3.2%)

Saliba F, Duvoux C, Gugenheim J, et al. Am J Transplant 2017;17(7):1843-1852.

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Alternative & Novel Maintenance Immunosuppression Regimens

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Extended Release Tacrolimus Regimens

	Feng, et al	Alloway, et al	von Einsiedel, et al
Design	Randomized study	Phase II, prospective, 3-sequence, open-label, multicenter study	Observational study
Population	De novo LT recipients (n=58)	Stable, adult LT patients (n=57)	Adult, LT patients on IR-TAC for at least 1 month (n=121)
Intervention	LCP-TAC (n=29) IR-TAC (n=29)	Converted to LCP-TAC on day 8 with PK assessment at day 14 and 21; 6 month extension evaluated PK and safety	LCP-TAC (n=61) IR-TAC (n=60)
Results	<ul style="list-style-type: none"> Similar PK outcomes Comparable safety and efficacy 	<ul style="list-style-type: none"> LCP-TAC total daily dose is about 30% less than IR-TAC LCP-TAC has significantly lower peak and peak-trough fluctuations than IR-TAC 	<ul style="list-style-type: none"> LCP-TAC group had 50% increase in concentration/dose ratio at 12 months (p<0.001) LCP-TAC group has improved eGFR at 6 months (p=0.029)

Feng S, Chapman WC, DuBay D. Am J Transplant 2012;12(Suppl. S3):239. Alloway RR, Eckhoff DE, Washburn KW, et al. Liver Transpl 2014;20(5):564-575.
 von Einsiedel J, Tholking G, Wilms C, et al. J Clin Med 2020;9(6):1-15.

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Belatacept Regimens

	Klntmalm, et al	LaMattina, et al
Design	Randomized, partially blinded, active-controlled, parallel group multicenter	Retrospective, single center experience
Population	<i>De novo</i> adult LT recipients (n=260)	<i>De novo</i> adult LT recipients with HCV and peri-op renal dysfunction (n=7)
Intervention	3 belatacept regimens compared to TAC monotherapy and TAC + MMF	<ul style="list-style-type: none"> Conversion to belatacept by POD14 Various concomitant ISP agents
Results	<ul style="list-style-type: none"> More patients in the belatacept groups experienced ACR, graft loss, and death at 6 months Study was terminated 	<ul style="list-style-type: none"> All patients recovered renal function Graft and patient survival was 100% while on belatacept therapy Possible bridge therapy option

Belatacept Black Box Warning:

- Not recommended for use in liver transplant patients due to increased risk of graft loss and death

Klntmalm GB, Feng S, Lake JR, et al. Am J Transplant 2014;14(8):1817-1827.
 LaMattina JC, Jason MP, Hanish SI, et al. Transplantation 2014;97(2):133-137.

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Unique Maintenance Regimens

	Steroid-free Regimen	MMF Monotherapy
Design	Prospective, randomized, open-label multicenter study (18 US Centers)	Prospective, randomized single center experience (Germany)
Population	Adult HCV-positive LT recipients (n=295)	Adult LT recipients (n=142)
Intervention	3 treatment groups: <ul style="list-style-type: none"> TAC + steroids (n=77) MMF + TAC + steroids (n=72) Daclizumab + MMF + TAC (n=146) 	2 treatment groups: <ul style="list-style-type: none"> CNI standard therapy (n=70) MMF monotherapy (n=72)
Results	<ul style="list-style-type: none"> No significant differences in ACR, hepatitis C virus (HCV) recurrence, patient or graft survival rates No difference in side effects of regimens 	<ul style="list-style-type: none"> No significant difference in ACR Graft and patient survival was same No difference in adverse effects

Klintmalm GB, Davis GL, Teperman L, et al. Liver Transplant 2011;17(12):1394-1403.

Schmeding M, Kiessling A, Neuhaus R, et al. Transplantation 2011;92(8):923-929.

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mTOR Inhibitor Regimens in Patients with HCC

	Geissler, et al	Rodriguez-Peralvarez, et al
Design	Prospective, randomized, open-label international study	Prospective observational study conducted at two centers in Spain
Population	Adult LT recipients with HCC (n=525)	Adult LT recipients within Milan criteria (n=192)
Intervention	Randomized at 4-6 weeks post-LT <ul style="list-style-type: none"> mTOR inhibitor free therapy (n=264) SRL-based therapy (n=261) 	<ul style="list-style-type: none"> Reduced dose TAC, EVR, and steroid taper (stopped within 6 months) Compared to historical controls without EVR
Results	No significant difference in recurrence-free survival between groups	Tumor recurrence rates were similar between treatment groups

Geissler EK, Schnitzbauer AA, Zulke C, et al. Transplantation 2016;100(1):116-125.

Rodriguez-Peralvarez M, Guerrero M, Barrera L, et al. Transplantation 2018;102(12):2056-2064.

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Therapeutic Drug Monitoring (TDM) Considerations

Effective Level of Immunosuppression Varies Based of Patient Specific Factors				
Drug Class	CNIs		mTOR Inhibitors	
Medications	Cyclosporine	Tacrolimus	Sirolimus	Everolimus
Goal whole blood trough levels (3 months after LT)*	100-200 ng/mL	5-10 ng/mL	5 ng/mL	3-8 ng/mL
Frequency of TDM Varies Based on				
• Time from transplant		• Patient specific factors		
• Pharmacokinetic drug properties		• Center-specific protocols		

*Ranges of goal whole blood trough levels vary between references and this table incorporates the broadest range

Lucey MR, et al. Liver Transpl 2013;19(1):3-26.

Charlton M, et al. Transplantation 2018;102(5):727-743.

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Question 1: JS is a 46 year old woman underwent deceased donor liver transplant yesterday for ESLD caused by primary biliary cirrhosis. Her past medical history is significant for GERD and HTN. Her laboratory results show improving liver function tests and are otherwise unremarkable. **Which of the following is the best immunosuppression regimen to start immediately post-transplant for this patient?**

- A. High-dose belatacept and mycophenolate
- B. Sirolimus, mycophenolate mofetil and prednisone
- C. Tacrolimus, mycophenolate mofetil and prednisone
- D. Everolimus, mycophenolate mofetil and prednisone

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- D. Everolimus, mycophenolate mofetil and prednisone

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Question 2: JS is now 5 weeks post-DDLT for ESLD caused by primary biliary cirrhosis. She returns to clinic and inquires about immunosuppression regimens that may help her preserve her renal function without significantly impacting patient and graft survival. Her recent laboratory results reveal Na 142, K 5.1, Cl 102, CO₂ 24, BUN 18, SCr 1.4, fasting plasma glucose 210 and tacrolimus trough level of 9.8 ng/mL. Her liver function tests and lipid panel are within normal limits. A recent urinalysis was negative for protein. **Which of the following immunosuppression regimens would you consider for this patient to help preserve her renal function?**

- A. MMF monotherapy
- B. Everolimus, low-dose tacrolimus and prednisone
- C. High-dose belatacept and mycophenolate
- D. Cyclosporine, mycophenolate mofetil and prednisone

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- D. Cyclosporine, mycophenolate mofetil and prednisone

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Key Takeaways

- No standardized maintenance immunosuppression regimen
 - Majority of LT recipients receive triple drug regimens with TAC, MMF, and steroids
- Individualization of maintenance regimens is common
 - Consideration of patient comorbidities
 - Adjustments related to immunosuppression related toxicities

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Maintenance Immunosuppression

Part Two - Liver Transplantation

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Maintenance of Immunosuppression Part Two – Pancreas and Islet Cell Transplantation

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Disclosures

- Speaker's Bureau – Veloxis Pharmaceuticals (ended April 2021)

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Learning Objectives

- Design a maintenance immunosuppression regimen for the prevention of rejection after pancreas transplant.
- Design a maintenance immunosuppression regimen for the prevention of rejection after islet cell transplant.

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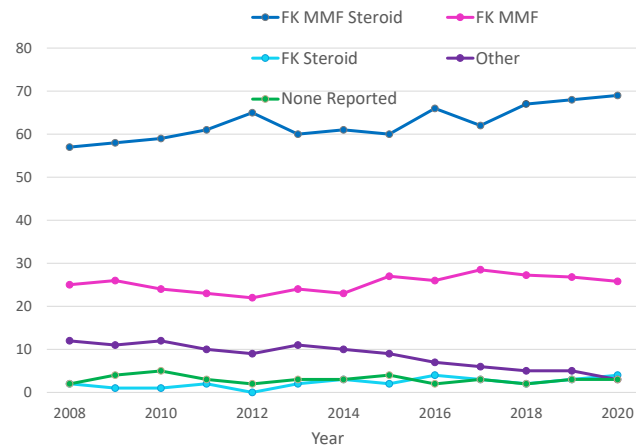
Pancreas Transplant Maintenance Immunosuppression

FK – tacrolimus
CYA – cyclosporine
MMF – mycophenolate mofetil
MPS – mycophenolate sodium
AZA – azathioprine
SIR – sirolimus
EVR - everolimus

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Trends in Maintenance Immunosuppression

- Majority utilizes a triple therapy regimen
 - Tacrolimus
 - Mycophenolate
 - Steroids
- Steroid-free regimen in 25.8%
- Incorporation of mTOR inhibitors or belatacept not well adopted



Am J Transplant 2022;22(S2):137-203

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Common Agents - Literature Highlights

Choice of CNI

- Cyclosporine vs. Tacrolimus

Choice of Antimetabolite

- Azathioprine vs. Mycophenolate

Steroids

- Early Steroid Withdrawal
- Late Steroid Withdrawal
- Steroid Avoidance vs. Steroid Withdrawal

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EuroSPK 001 Trial

- Tacrolimus vs Cyclosporine, modified
 - Randomized 1:1 (103 FK, 102 CYA)
 - FK (8-15ng/mL, 5-10ng/mL)
 - CYA (150-250ng/mL, 100-200ng/mL)
 - MMF 2-3 g/day
 - Steroids tapered over 3 mo, off by 6 mo
 - Induction – rATG 1.25 mg/kg x 4
 - Primary endpoints
 - BPAR of either pancreas or kidney at 1 year
 - Treatment failure for any reason

- Results

	FK	CYA	p-value
BPAR 1 year	27.2%	38.2%	0.09
Mod/Severe rejection	1%	12%	0.0053
Treatment failure	23.3%	52.9%	NR
Pancreas survival 1 year	91.3%	74.5%	0.0014

- Changes in therapy

– Cyclosporine n=34 vs Tacrolimus n=6

	FK	CYA
Fasting Glucose (mM/L)	4.93 ± 0.78	5.37 ± 2.18
C-peptide (nM/L)	1.13 ± 0.53	1.23 ± 0.76
A1c (%)	5.4 ± 0.7	5.6 ± 1.3

Transplantation 2004;8:1221-8

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EuroSPK 003 Trial

- 3-year results of EuroSPK 001
 - FK, n=103
 - CYA, n=102
 - rATG induction, MMF, and steroid withdrawal
- Results
 - Study withdrawals
 - 36.9% FK vs 57.8% CYA, p=0.003
 - Rejection
 - 41 patients (59 episodes) FK vs 51 patients (73 episodes) CYA

	FK	CYA	p-value
Rejection-free survival (%)	54.2	43.7	NS
Mod/Severe rejection (%)	3.2	28.2	0.009
Pancreas graft survival (%)	89.2	72.4	0.002
Graft loss – thrombosis, n	2	10	0.02
A1c (%)	5.2 ± 0.7	5.0 ± 0.6	0.02
A1c ≥ 6% (%)	11.3	2.9	NR

- Adverse events similar between arms
 - CV events, UTI, CMV, peritonitis, polyomavirus nephropathy

Transplant Proc 2005;37:2843-5

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Common Agents - Considerations

Choice of CNI

- Cyclosporine vs. Tacrolimus

Tacrolimus

- Decreased incidence of BPAR (kidney or pancreas)
- Less treatment failure
- Less severe rejection
- Less non-immunologic graft loss
- Decreased rejection risk (kidney allograft) not seen in context of non-depleting induction
 - 28% FK vs. 4.5% CYA
 - No difference in pancreas allograft rejection

Tacrolimus XR

- Single center reports of use in pancreas transplant patients

Transplant Proc 2005;37:2641-3

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Antimetabolites

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Mycophenolate vs Azathioprine in SPK

- MMF vs AZA in SPK, n=358
- Induction
 - OKT3 or equine ATG
- Cyclosporine-based regimen
- **MMF 3gm/day (n=109) vs AZA 2mg/kg/day (n=249)**
- Outcomes
 - Patient and graft survival
 - Rejection rates

Results

	MMF	AZA	p-value
Kidney BPAR, %	31	75	0.0001
Pancreas rejection, %	7	24	0.003
Steroid refractory rejection, %	15	52	0.01
2-yr kidney graft survival, %	95	86	<0.05
2-yr pancreas graft survival, %	95	83	<0.05

- Surgical infections more common in MMF
- No difference in common viral, bacterial, or fungal infections

Transplantation 1998;66:1751-9

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Mycophenolate vs Azathioprine

- MMF n=54 vs AZA n=57
 - Induction
 - OKT3 5mg/day x 7-14 days
 - ATGAM 5-30mg/kg/day x 7-14 days
 - Maintenance
 - Methylprednisolone 500mg IV x 2 then taper to 0.3 mg/kg
 - SPK/PAK: CYA (300-350 ng/mL)
 - PTA: FK (15-20 ng/mL)
 - **MMF 2gm/day vs. AZA 100mg daily**
- Primary Outcome
 - Patient and Graft survival at 6 months

Results

- SPK 59%, PAK 33%, PTA 8%

	MMF	AZA	p-value
BPAR, n (%)	24 (46)	37 (69)	0.01
Severe BPAR, n (%)	4 (7)	15 (26)	0.005
Antibody treatment, n (%)	16 (30)	32 (56)	0.004
Graft survival, %	91	88	0.29
Patient survival, %	97	96	0.57

- GI-related adverse effects more common with MMF
- Drug discontinuation similar

J Clin Pharmacol 2001;41:861-9

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Common Agents - Considerations

Choice of Antimetabolite

- Azathioprine vs. Mycophenolate

Mycophenolate

- Decreased incidence of BPAR
- Less severe rejection
- Variable reports of improved graft survival
- Increased incidence of side effects
 - GI
 - Infections

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Steroid-Sparing Strategies

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Early Steroid Withdrawal

- Solitary Pancreas
 - Steroid Withdrawal (SW) at 21 days (n= 22) vs. maintenance steroids (MS) 5mg daily (n=32)
 - rATG 1.5mg/kg x 7-10 days
 - MMF 1000mg BID, FK (12-15ng/mL)
- Outcomes at 1 year
 - BPAR
 - Graft survival
 - Patient survival

- Results

	SW	MS	p-value
BPAR, %	27.3	37.5	0.56
Graft Survival, %	95.5	81.2	0.13
Patient survival, %	100	93.8	0.23

- Re-initiation of steroids in 41%
- MS - Increase in infections and infectious-related complications requiring changes in therapy
 - 78% vs 50%, p=0.04

Clin Transplant 2007;21:491-7

95

Late Steroid Withdrawal

- T1DM SPK recipients, n = 77
 - Fresenius ATG 3mg/kg x 7-10 days
 - FK 0.1mg/kg BID, MMF 2gm/day
 - FK goal 8-14 ng/mL

Methylprednisolone	500 IV, 250 IV, 250 IV, 125 IV
Prednisone	1mg/kg/day, taper to 10mg by 3 months, further taper by 6 months, withdrawal by 12 mo

- Patients
 - 33.7 yo, 62.3% female, mean diabetes duration of 22.7 ± 5 years

- Results

- Rejection within 1 mo, n=11 (14.3%)
- Early pancreas or kidney loss, n=12/2
- Steroid withdrawal in 42/54 (77.8%)

Steroid Free	2 years	5 years
Patient survival	100%	98%
Kidney survival	98%	98%
Pancreas survival	95%	90%

- No differences in fasting BG or A1c between those on and off steroids

Transplant Proc 2009;41:909-12

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Steroid Withdrawal (SW) vs. Steroid Avoidance (SA)

- Randomized 1:1 (25 SW, 25 SA)
 - SW: MP 500 mg IV x 1, Prednisone taper to maintenance dose of 10 mg daily, off by day 90
 - SA: None
 - Induction – rATG x 10 d
 - CYA (150-250 ng/mL), MMF 1000 mg BID
- Primary endpoint
 - BPAR at 1 year

- Results
 - SW: 76% remained steroid-free
 - SA: 80% never received steroids

	SW	SA
Rejection (Kidney), n (%)	1 (4)	2 (8)
1 year patient survival, %	100	96
1 year kidney survival, %	100	96
1 year pancreas survival, %	88	88

- Less UTI, more bronchopulmonary infections in SA arm
- No difference in fasting BG, A1c, or lipids at 1 year
- Serum creatinine higher in SA

Am J Transplant 2005;5:1332-8

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Common Agents - Considerations

Steroid Sparing Strategies

- Similar
 - Rates of rejection
 - Pancreas graft survival
 - Patient survival
- May be associated with less infections
- Improvement in metabolic outcomes not well defined
- Reinitiation of steroids
 - Rejection
 - Intolerance/discontinuation of other immunosuppressive agents

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Alternative Agents

mTOR Inhibitors

Belatacept

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Sirolimus vs Mycophenolate 10-year Study

- SIR (n=84) vs MMF (n=86) in SPK
 - Induction
 - Daclizumab 1mg/kg x 2
 - rATG 1mg/kg x 5
 - FK (5-7 ng/mL), Steroids 0.05 mg/kg daily by 3 mo
 - SIR (5-7 ng/mL) or MMF 1000 mg BID
- Outcomes
 - Kidney and Pancreas BPAR
 - Graft survival, patient survival
 - Infection

Results

	SIR	MMF	p-value
Kidney rejection 1 yr, n (%)	0 (0)	10 (12)	0.001
Pancreas rejection 1 yr, n (%)	1 (1)	7 (8)	0.04
Patient survival 10 yrs, %	67	73	0.99
Pancreas graft survival, %	98	84	0.12

- Drug discontinuation
 - MMF (52%) vs SIR (29%)
- C-peptide similar, A1c lower with MMF (p=0.00004)
- No differences in CMV, BK, or EBV infection

Am J Transplant 2012;12:3363-76

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EUROSPK 002 Trial 5-year Data

- Sirolimus vs. MMF
 - Randomized 1:1 (SIR 107, MMF 115)
 - SIR goal 5-10 ng/mL
 - MMF 1000 mg BID
 - FK 0.5 mg/kg BID (10-15 ng/mL x 1 mo, then 5-10 ng/mL)
 - Steroids withdrawn by 6 weeks
 - Induction rATG 18 mg/kg
- Primary Endpoints
 - 5-year pancreas graft survival – death, explant, retransplant, use of insulin at any dose for > 30 days

Results

	SIR	MMF	p-value
Pancreas survival, noncensored, %	76.4	71.6	> 0.05
Death-censored pancreas survival, %	83.9	72.9	0.037
Thrombosis, n	8	10	0.829
Rejection, n	5	10	0.193
Thrombosis + Rejection, n	1	7	0.076

- Mean serum creatinine higher with SIR vs MMF at 4-year follow-up
- No difference in patient survival

Am J Transplant 2020;20:779-87

101

CTOT-15 Belatacept in Steroid and CNI Withdrawal

- SPK Randomized (1:1) to belatacept-based vs CNI-based
 - rATG 6 mg/kg
 - MMF or MPS, off steroid by POD 5
 - FK (8-12 ng/mL x 24 weeks, then 5-8 ng/mL)
 - Belatacept 10 mg/kg POD 5, 14, 28, 56, 84, belatacept 5 mg/kg monthly
 - FK (5-8 ng/mL x 24 weeks, 3-5 ng/mL to week 40), then withdrawal
- Primary Outcome – GFR at 52 weeks

Results

- Renal function similar
- Estimated difference + 2.1 ml/min, p=0.75

	FK (n=21)	Belatacept (n=22)
Full graft function, n (%)	21 (100)	19 (86.4)
Graft loss, n (%)	0	1 (4.5)
BPAR, Kidney grade \geq 1A, n (%)	2 (9.5)	2 (9.1)
BPAR, Pancreas grade \geq 1, n (%)	1 (4.8)	5 (22.7)
Treated rejection, n (%)	3 (14.3)	8 (36.4)
AMR, n (%)	0	0
A1c, mean \pm SD	5.3 \pm 0.48	5.5 \pm 1.57

Am J Transplant 2020;20:1668-78

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Alternative Agents

mTOR Inhibitors	Belatacept
<ul style="list-style-type: none"> Decreasing trends in de novo use <ul style="list-style-type: none"> Undesirable side effects in the initial transplant period Commonly used for conversion <ul style="list-style-type: none"> In place of either calcineurin inhibitor or antimetabolite Antiviral, antiproliferative properties 	<ul style="list-style-type: none"> Increased pancreas graft rejection No difference in diabetes or metabolic outcomes

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Islet Cell Transplant Maintenance Immunosuppression

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Edmonton Protocol

- T1DM, C-peptide < 0.48ng/mL, n=7
 - Induction
 - Daclizumab 1 mg/kg Q14 days x 5
 - Maintenance
 - FK 1 mg BID (3-6 ng/mL)
 - SIR 0.2 mg/kg x 1, 0.1 mg/kg (12-15 ng/mL for 3 mo, then 7-10 ng/mL)
 - Steroid Free
 - Standard islet preparations, infusions
- Measurements
 - Fluctuations in BG, OGTT, mixed meal measurements, A1c, C-peptide
- Results
 - 6/7 required 2nd infusion, median 29 days
 - 1/7 required 3rd infusion
 - Infusion to gain II – 11,547 ± 1604 IE/kg
 - Insulin requirements decreased in all 7
 - Normal A1c
 - Detectable C-peptide (p<0.001)
 - OGTT
 - 5 impaired responses (BG 142-195)
 - 2 FG elevated (BG ≥ 110)
 - Last follow-up – 100% free of insulin

NEJM 2000;343:230-8

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Edmonton Protocol 5-year Follow-Up

- N=65
- 2 transplants n=52, 3 transplants n=11
 - Mean age 42.9 years, duration of diabetes 27.1 years, 57% women
- Results
 - Mean islets/procedure 393,554 ± 10,528 IE/kg
- Results
 - C-peptide secretion 25.2 mo
 - Mouth ulcerations 89%, diarrhea 60%, change to MMF in 12% due to edema
 - Graft survival ~80% at 5 years
 - Insulin independence ~10% at 5 years

	1 st Infusion	2 nd Infusion	3 rd Infusion
Insulin independence	N=5 502,211 ± 79,770 IE/kg	N=33 792,396 ± 27,867 IE/kg	N=6 987,820 ± 47,463 IE/kg

Diabetes 2005;54:2060-9

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Trends in Maintenance Immunosuppression

Maintenance	ITA, n (%)	IAK, n (%)	1999-2002, n (%)	2003-2006, n (%)	2007-2010, n (%)	2011-2014, n (%)	2015-2018 n (%)
mTOR, CNI, MPA	106 (14.7)	28 (18.3)	36 (21.6)	49 (19.3)	27 (13)	22 (9.4)	
mTOR, CNI	320 (44.3)	54 (35.3)	109 (6.3)	156 (61.4)	72 (34.8)	37 (15.8)	
mTOR, MPA	16 (2.2)			7 (2.8)	9 (4.3)		
CNI, MPA	215 (29.8)	58 (37.9)	18 (10.8)	36 (14.2)	75 (36.2)	133 (56.8)	11 (84.6)
mTOR	11 (1.5)			1 (0.4)	10 (4.8)		
CNI	19 (2.6)	8 (5.2)	1 (0.6)	1 (0.4)	4 (1.9)	21 (9)	
MPA	25 (3.5)	1 (0.7)	3 (1.8)	4 (1.6)	7 (3.4)	10 (4.3)	2 (15.4)
Missing/Unknown	10 (1.4)	4 (2.6)			3 (1.4)	11 (4.7)	
Total	722 (100)	153 (100)	167 (100)	254 (100)	207 (100)	234 (100)	14 (100)

www.citregistry.org. Accessed March 27, 2022

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Question 1: Which of the following statements is true of steroid withdrawal protocols?

- A. Steroid withdrawal demonstrates inferior pancreas graft survival
- B. Early steroid withdrawal has shown superior graft survival compared to late steroid withdrawal
- C. Common reason for reinitiation of steroids is due to rejection
- D. Majority of patients post-pancreas transplant are on steroid withdrawal protocols

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Question 2: Patient AG is undergoing an islet cell transplant for T1DM at a center with a newly established transplant program. Design a maintenance immunosuppression regimen that is in line with the original Edmonton Protocol.

- A. Tacrolimus (goal 5-10 ng/mL) + Mycophenolate mofetil 1gm BID
- B. Tacrolimus (goal 3-6 ng/mL) + Sirolimus (12-15 ng/mL)
- C. Tacrolimus (goal 5-10 ng/mL) + Mycophenolate mofetil 1gm BID + Prednisone taper
- D. Tacrolimus (goal 3-6 ng/mL) + Sirolimus (12-15 ng/mL) + Prednisone taper

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Key Takeaways

- Majority of pancreas transplant recipients receive a triple-therapy regimen consisting of tacrolimus, mycophenolate, and prednisone
- Early or late steroid withdrawal occurs in approximately 25% of recipients after pancreas transplant
- Standard of care in islet cell transplantation is a steroid-free maintenance immunosuppression regimen. Current practices employ a tacrolimus and mycophenolate combination.

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Maintenance of Immunosuppression Part Two – Pancreas and Islet Cell Transplantation

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Maintenance of Immunosuppression Part Two - Heart Transplantation

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Disclosures

- No relevant financial disclosures



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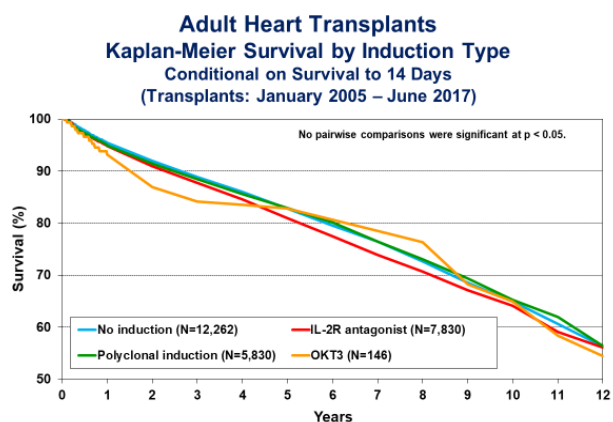
Learning Objectives

- Describe common immunosuppression approaches in heart transplantation.
- Discuss alternate approaches to immunosuppression.

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Heart Transplant Induction Immunosuppression Basics

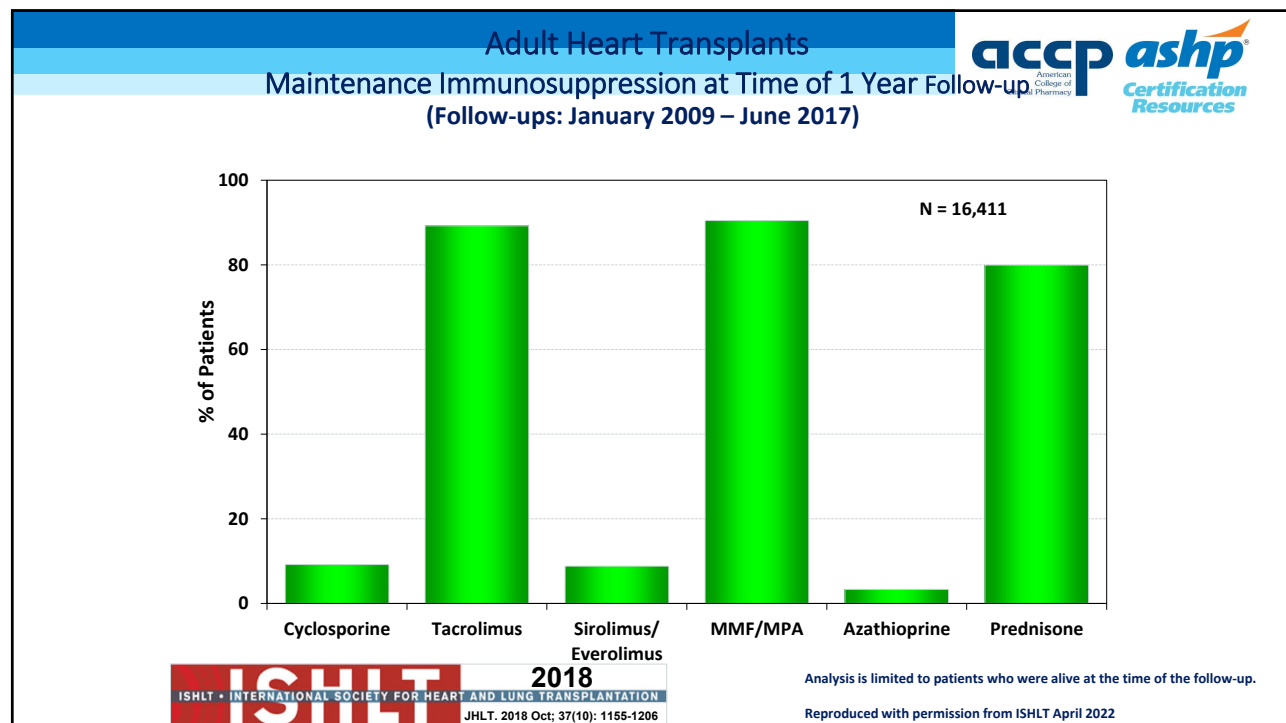
- Induction
 - No survival benefit
 - Largely center specific
 - May be beneficial in sensitized patients



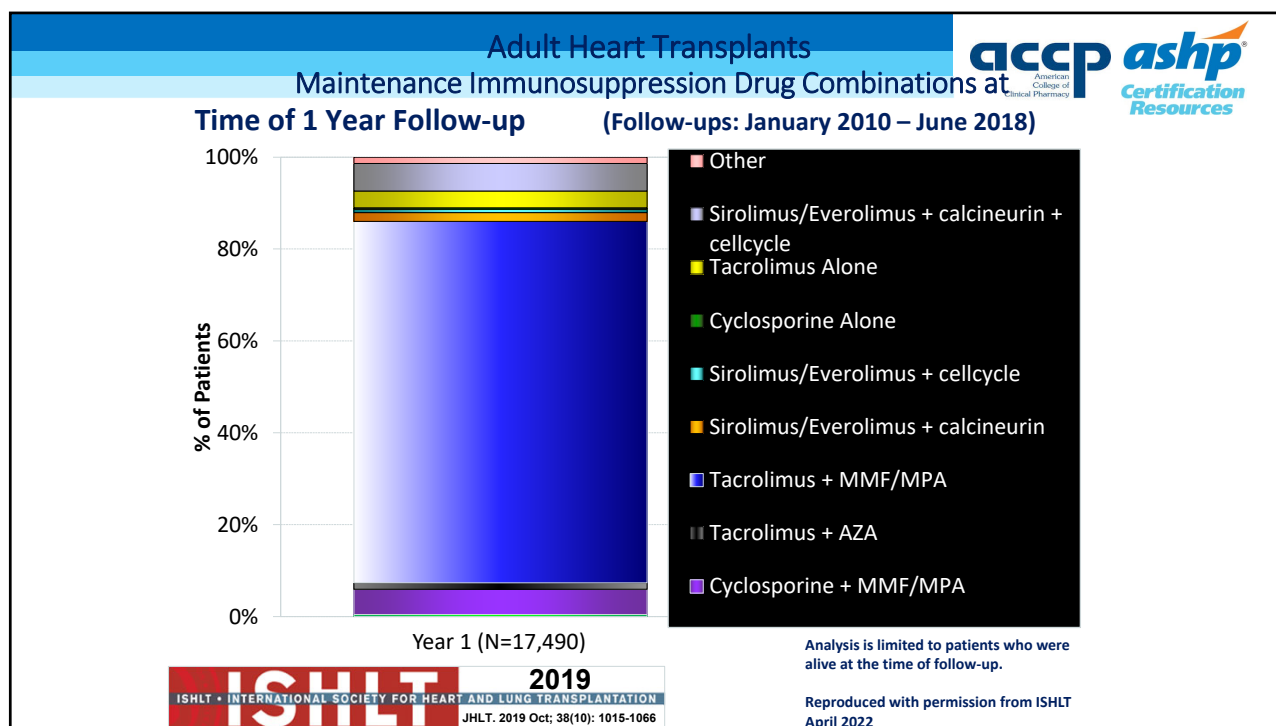
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Common Maintenance Combinations

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Current Practice

- ISHLT guidelines recommends CNI based regimen initially
 - Tacrolimus based regimens have lower rejection rates
 - Once daily preparation carry no recommendation
- Denovo mTOR's as a replacement for a CNI are associated with increased rejection and not recommended
- Mycophenolate mofetil or Mycophenolic acid generally serve as the second agent
 - MMF vs. AZA based regimens demonstrate less rejection, decreased CAV, and increased survival
 - Regular mTOR use as a second agent without a compelling indication is still actively debated
- Corticosteroids use, dose and duration is program specific with varying outcomes in the literature

J Heart Lung Transplant 2010 Aug;(29):914-56
J Heart Lung Transplant 2018 Oct;37(10):1155-1168
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Historic Heart Transplant Trials

Table 8 Significant Differences in Primary End Points between Study Groups from Major Clinical Trials

Author (year)	Study	N	Follow-up	Survival	Rejection	CAV by IVUS
Kobashigawa ¹⁶³ (1998)	MMF vs AZA	650	3 years	MMF = higher survival ^a	MMF = less rejection	NS; MMF = less CAV at 1 year ^b
Reichert ²⁰⁹ (1998)	TAC vs CYA	82	1 year	NS	NS	
Taylor ¹⁵³ (1999)	TAC vs CYA	85	1 year	NS	NS	
Eisen ¹⁵⁷ (2003)	EVL vs AZA	634	1 year	NS	EVL groups = less rejection	EVL groups = less CAV
Keogh ¹⁵⁶ (2004)	SRL vs AZA	136	2 years	NS	SRL groups = less rejection at 6 months	SRL groups = less CAV
Grimm ¹⁵⁴ (2006)	TAC vs CYA	314	1.5 year	NS	TAC = less rejection at 6 months	...
Kobashigawa ¹⁵⁸ (2006)	TAC/MMF vs TAC/SRL vs CYA/MMF	343	1 year	NS	NS; TAC groups = lower any-treated rejection	...
Baran ¹⁵⁹ (2007)	TAC/MMF vs TAC	58	1 year	NS	NS	NS
Lehmkuhl ¹⁶⁰ (2008)	EVL/rd-CYA vs MMFsd-CYA	176	1 year	NS	NS	...

CAV, cardiac allograft vasculopathy; CYA, cyclosporine; EVL, everolimus; EVL/rd, everolimus/reduced exposure; IVUS, intravascular ultrasound; MMF, mycophenolate mofetil; MMFsd, mycophenolate mofetil/standard exposure; NS, not statistically significant; SRL, sirolimus; TAC, tacrolimus.

^aTreated-patient population (see text).

^bReanalysis of MMF IVUS data.²⁰⁰

J Heart Lung Transplant 2010 Aug;(29):914-56

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Question 1: Which of the following statements is true regarding maintenance immunosuppressive strategies in Heart Transplantation?

- The most common immunosuppression combination at 1 year after transplant is Tacrolimus +Mycophenolate Mofetil+ prednisone
- Cyclosporine has been shown to decrease rejection compared to tacrolimus
- Azathioprine has been shown to have survival benefits compared to Mycophenolate Mofetil
- Everolimus is the most common maintenance immunosuppressant 1 year after transplant

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Question 1: Which of the following statements is true regarding maintenance immunosuppressive strategies in Heart Transplantation?

- The most common immunosuppression combination at 1 year after transplant is Tacrolimus +Mycophenolate Mofetil+ prednisone
- Cyclosporine has been shown to decrease rejection compared to tacrolimus
- Azathioprine has been shown to have survival benefits compared to Mycophenolate Mofetil
- Everolimus is the most common maintenance immunosuppressant 1 year after transplant

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Alternate Combinations

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Heart Transplant Alternate Immunosuppression

- Alternate combinations
 - Center specific use common
 - Common indications for changing meds
 - Renal function
 - Cancer
 - CAV
 - Intolerance
 - Rejection

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Role of mTOR

- ISHLT guidelines state: "MMF, EVL, or SRL" as tolerated should be included in contemporary immunosuppressive regimens..."
- Studies have demonstrated benefits or relative safety in each of the following regarding mTOR use
 - Potential mortality benefit
 - Declining renal function- CNI replacement or dose reduced
 - Cancer- CNI replacement
 - CAV- CNI replacement, add on therapy, or antiproliferative replacement
 - Intolerance- Replacement if MMF
 - Rejection-add on therapy or antiproliferative replacement

J Heart Lung Transplant 2010 Aug;(29):914-56
 J Am Coll Cardiol 2019; 73(21): 2676-2699 J Am Coll Cardiol. 2018;71(6): 636-650
 Am J Transplant 2013;13(5):1203-16 Clin Transplant 2012; 26: 42-49

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CNI free with Sirolimus

- CNI free using SRL vs Standard CNI
 - All initiated on CNI
 - CNI n=134 patients
 - SRL N=268 patients
- Endpoints
 - Progression of CAV
 - All cause mortality
 - CAV mortality
 - CAV related events
- Results
 - SRL arm significantly lower in all endpoints
 - Clinical benefits greatest if converted early post transplant (6mo- 2 y)

J Am Coll Cardiol. 2018;71(6): 636–650

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Effect of Conversion to SRL Compared with CNI based Immunosuppression

Outcome	HR(95% CI) for SRL relative to CNI	p-value
All-cause death		
Unadjusted	0.51 (0.34-0.75)	0.0007
Adjusted	0.34 (0.31-0.70)	0.0002
CAV-associated death		
Unadjusted	0.22 (0.09-0.47)	0.0003
Adjusted	0.27 (0.11-0.61)	0.0025
Nonfatal CAV events		
Unadjusted	0.32 (0.18-0.56)	<0.0001
Adjusted	0.35 (0.19-0.61)	0.0002
All CAV-associated events		
Unadjusted	0.33 (0.19-0.54)	<0.0001
Adjusted	0.35 (0.21-0.59)	<0.0001
Composite all cause death and CAV associated events		
Unadjusted	0.48 (0.34-0.68)	<0.0001
Adjusted	0.45 (0.32-0.65)	<0.0001

J Am Coll Cardiol. 2018;71(6): 636–650

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Everolimus vs MMF as a second agent

	Month 12			Month 24		
	Everolimus 1.5 mg n=282 (%)	MMF 3g n=271 (%)	Difference % (95% CI)	Everolimus 1.5 mg n=282 (%)	MMF 3g n=271 (%)	Difference % (95% CI)
Composite efficacy failure*	99(35.1)	91(33.6)	1.5 (-7.5, 10.6)	111(39.4)	112(41.3)	-2.0 (-11.3, 7.4)
<i>BPAR- ISHLT 2R</i>	63(22.3)	67(24.7)	-2.4 (-9.5, 4.7)	68(24.1)	74(27.3)	-3.2 (-10.5, 4.1)
<i>ACR with hemodynamic compromise</i>	11(3.9)	7(2.6)	1.3 (-1.6, 4.3)	12(4.3)	14(5.2)	-0.9 (-4.4, 2.6)
<i>Death</i>	22(7.8)	13(4.8)	3.0 (-1.0, 7.0)	30(10.6)	25(9.2)	1.4 (-3.6, 6.4)
<i>Graft Loss/retransplant</i>	4(1.4)	5(1.8)	-0.4 (-2.5, 1.7)	7(2.5)	10(3.7)	-1.2 (-4.1, 7.7)
<i>Lost to follow up</i>	9(3.2)	10(3.7)	-0.5 (-3.5, 2.5)	10(15.2)	14(5.2)	-1.6 (-5.0, 1.8)
<i>Acute rejection treated with antilymphocyte therapy</i>	13(4.6)	9(3.3)	1.3 (-2.0, 4.5)	14(4.1)	11(4.1)	0.9 (-2.6, 4.4)

* Composite incidence of ISHLT 2R rejection, ACR with hemo compromise, death, graft loss/retransplant, or loss to follow up

Adapted from Am J Transplant 2013;13(5):1203-16

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Belatacept in Heart Transplant

- Limited data exists-mainly in abstracts or retrospective observational studies
 - Primary indications
 - Renal dysfunction
 - CNI Intolerance
- Largest study
 - 40 patients retrospective multi-center observational study
 - Results
 - 76% CNI Free
 - GFR was improved (+59%, P = .0002)
 - Multiple rejections after conversion (more common in late converters)
 - 1 death
 - 16 discontinuations
 - 24 month follow up

Am J Transplant. 2020;20(2):553-563

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Common Immunosuppressive Regimens

Tacrolimus
or
Tacrolimus + Prednisone
or
Tacrolimus + MMF + Prednisone
or
Tacrolimus + mTOR
or
mTOR+MMF

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Question 2: Which of the following are true regarding use of mTOR's in Heart Transplant recipients?

- CNI free regimens using a mTOR decrease the risk of rejection
- CNI free regimens may improve renal function
- The addition of a mTOR decreases the risk of CAV
- Replacement of MMF with a mTOR is not recommended

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Question 2: Which of the following are true regarding use of mTOR's in Heart Transplant recipients?

- CNIs free regimens using a mTOR decrease the risk of rejection
- **CNI free regimens may improve renal function**
- **The addition of a mTOR decreases the risk of CAV**
- Replacement of MMF with a mTOR is not recommended

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Key Takeaways

- No difference in common Survival except when using MMF vs AZA
- Rejection rates are decreased with Tac vs CSA
- Once daily dosing of Tacrolimus carries no ISHLT recommendation
- Tacrolimus + MMF+ Prednisone is the standard immunosuppression combination for the majority of centers
- Denovo mTOR's as a replacement for a CNI are associated with increased rejection and not recommended
- Conversion to CNI free therapy using a mTOR may decrease risk of CAV, have renal benefits, reduce the risk of cancer and decrease all cause mortality
- Antiproliferative agent replacement with a mTOR does not increase the risk of rejection

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Maintenance of Immunosuppression Part Two - Heart Transplantation

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Maintenance of Immunosuppression Part Two - Lung Transplantation

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Disclosure

- I have financial relationships with Astellas (researcher) and Takeda (advisor).
- I will be discussing off-label medication uses.

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Learning Objectives

- Compare and contrast the benefit, risk, and role of each maintenance immunosuppressant medication in lung transplantation.
- Design evidence-based maintenance immunosuppression regimens for lung transplant recipients.

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Induction Immunosuppression in Lung Transplantation

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Cochrane Review: IL-2 RA vs No Induction

Outcome	Illustrative comparative risks		Relative effect (95% CI)	# participants (studies)	Quality of the evidence
	IL-2 RA (95% CI)	No induction			
Mortality Follow-up: 2 years	268 per 1000 (88-828)	400 per 1000	RR 0.67 (0.22-2.07)	25 (1)	moderate
Acute rejection Follow-up: 2 years	535 per 1000 (245-1000)	500 per 1000	RR 1.07 (0.49 to 2.33)	25 (1)	moderate
Bronchiolitis obliterans syndrome Follow-up: 2 years	132 per 1000 (28-596)	400 per 1000	RR 0.33 (0.07 to 1.49)	25 (1)	moderate

Penninga L, et al. *Cochrane Database of Systematic Reviews* 2013; 11: CD008927 including:
Conte JV. www.clinicaltrials.gov 2010.

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Cochrane Review: Polyclonal T-cell Antibody vs No Induction

Outcome	Illustrative comparative risk		Relative effect (95% CI)	# participants (studies)	Quality of the evidence
	Polyclonal Ab (95% CI)	No antibody			
Mortality Follow-up: 2-8 years	457 per 1000 (318-659)	448 per 1000	RR 1.02 (0.71-1.47)	125 (3)	moderate
Acute rejection \geq grade 2 Follow-up: 2-8 years	328 per 1000 (212-502)	483 per 1000	RR 0.68 (0.44 to 1.04)	125 (3)	moderate
Infection Follow-up: 2-8 years	642 per 1000 (445-921)	458 per 1000	RR 1.4 (0.97 to 2.01)	104 (2)	moderate
Bronchiolitis obliterans syndrome Follow-up: 2-8 years	433 per 1000 (305-620)	534 per 1000	RR 0.81 (0.57 to 1.16)	125 (3)	moderate

Penninga L, et al. *Cochrane Database of Systematic Reviews* 2013; 11: CD008927 including:
Chaparro C, et al. *JHLT* 1999; 46. Conte JV. www.clinicaltrials.gov 2010. Hartvig MG, et al. *JHLT* 2008: 547.

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Cochrane Review: Polyclonal T-cell Antibody vs IL-2 RA

Outcome	Illustrative comparative risk		Relative effect (95% CI)	# participants (studies)	Quality of the evidence
	Polyclonal Ab (95% CI)	IL-2 RA			
Mortality Follow-up: 0.5-2 years	160 per 1000 (62-412)	113 per 1000	RR 1.41 (0.55-3.64)	100 (3)	moderate
Acute rejection Follow-up: 1-2 years	698 per 1000 (488-1000)	525 per 1000	RR 1.33 (0.93 to 1.92)	76 (2)	moderate
Infection Follow-up: 1 year	801 per 1000 (625-1000)	880 per 1000	RR 0.91 (0.71 to 1.16)	50 (1)	moderate
Bronchiolitis obliterans syndrome Follow-up: 1-2 years	124 per 1000 (31-490)	75 per 1000	RR 1.66 (0.42 to 6.53)	76 (2)	moderate

Penninga L, et al. *Cochrane Database of Systematic Reviews* 2013; 11: CD008927 including: Conte JV. www.clinicaltrials.gov 2010. Mullen JC, et al. *JHLT* 2007; 504. Senn B, et al. *Eur Resp J* 2001; 179s.

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Additional agents: Alemtuzumab

Citation	Induction	N	Methods	Outcomes
Jaksch 2014	Alemtuzumab vs ATG	60	RCT	≥A2 AR: 0% vs 33%, p=0.019 Survival, 1-yr: 93% vs 96%, p=0.1 Survival, 2-yr: 90% vs 96%, p=0.1
Furuya 2016	Alemtuzumab vs basiliximab vs no induction	6117	Retrospective registry (UNOS)	Median survival 2321 vs 2352 vs 1967, p=0.001 BOS, 5-yr: 23% vs 55% vs 56% Items a/w survival on multivariate analysis: Alemtuzumab; HR 0.8 (0.67-0.95), p=0.009 Basiliximab; HR 0.88 (0.8-0.98), p=0.015
Benazzo 2019	Alemtuzumab vs ATG vs no induction	446	Retrospective	Freedom from AR, 5-yr: 97% vs 91% vs 80% Freedom from CLAD, 5-yr: 72% vs 85% vs 51% Survival, 5-yr: 77% vs 71% vs 63%

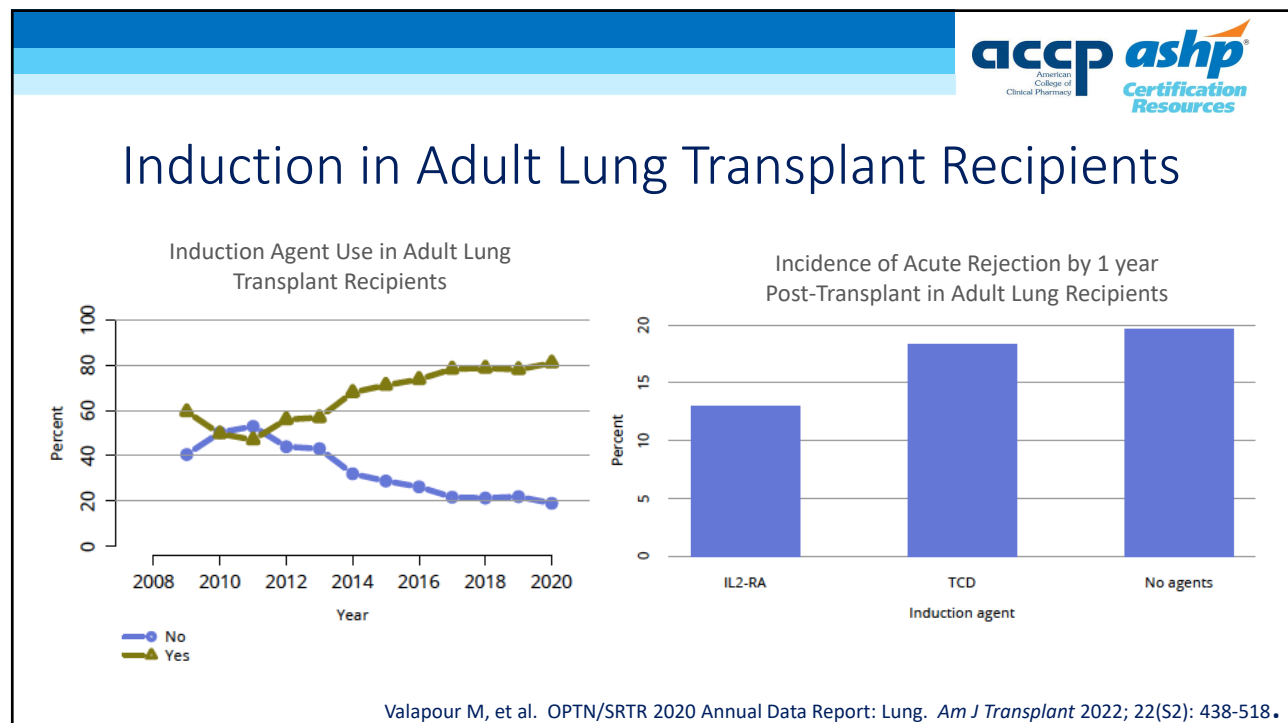
Jaksch P, et al. *Am J Transplant* 2014; 14: 1839-45. Furuya Y, et al. *Am J Transplant* 2016; 16(8): 2334-41. Benazzo A, et al. *PLoS ONE* 2019; 14(1): e0210443.

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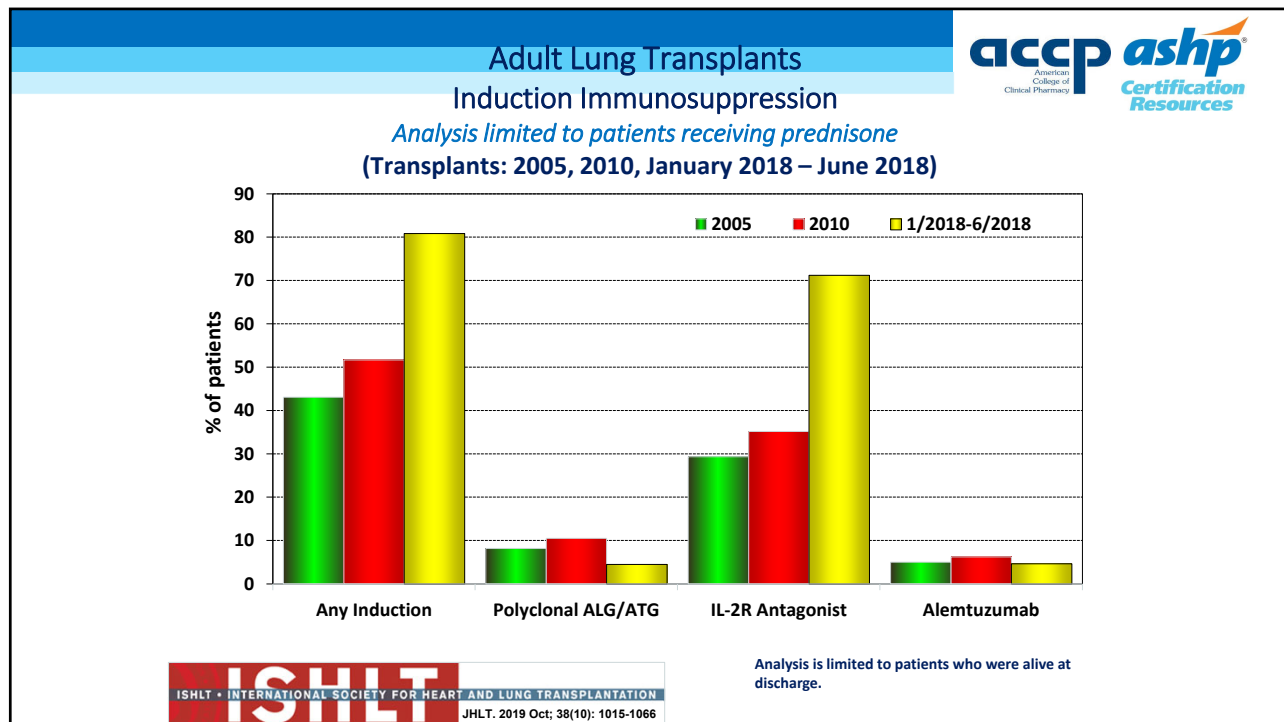
National and International Trends in Immunosuppressive Choices



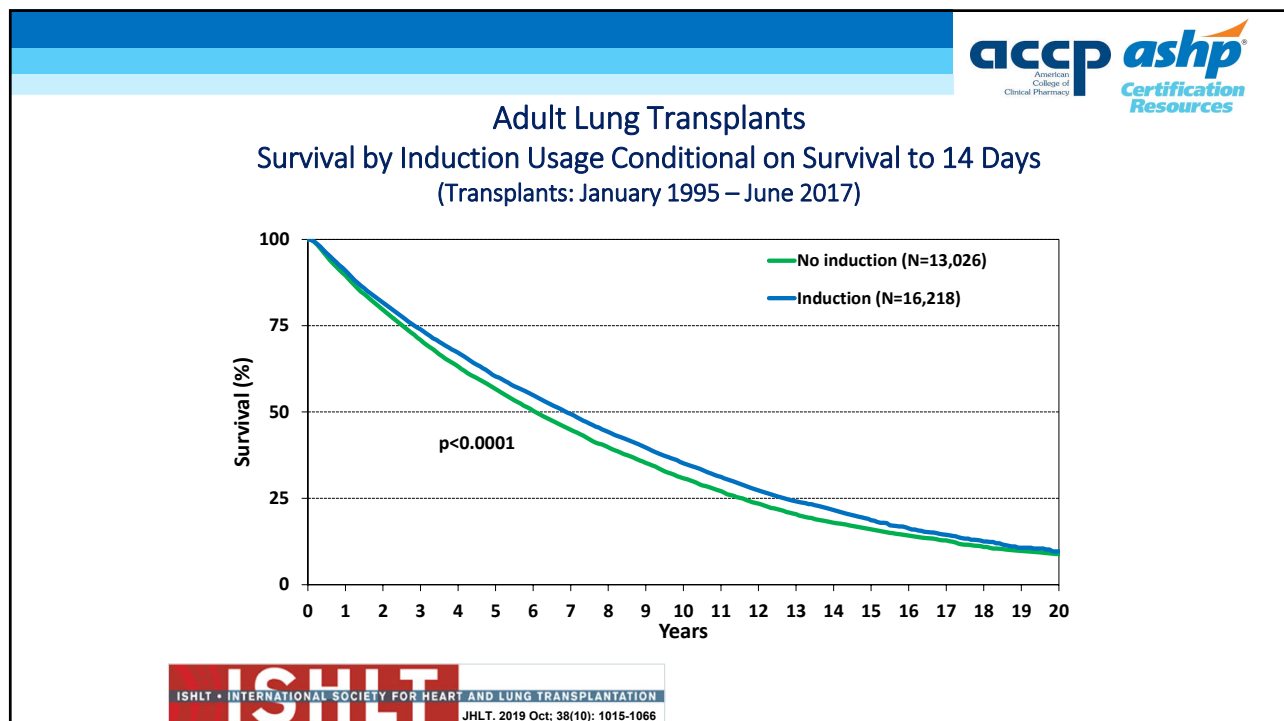
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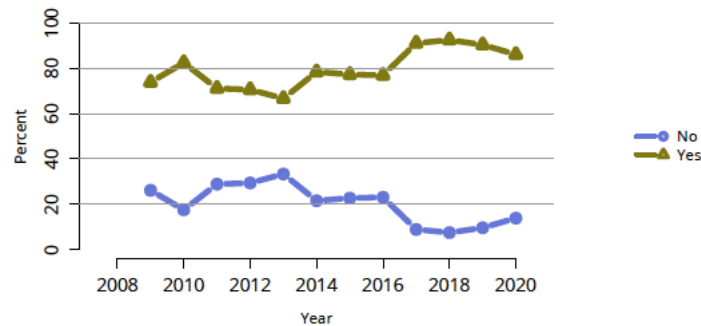


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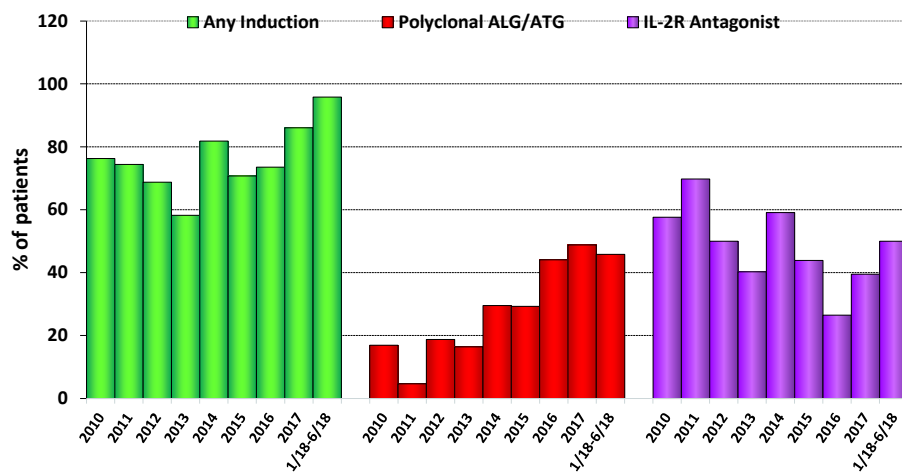
Induction in Pediatric Lung Transplant Recipients



Valapour M, et al. OPTN/SRTR 2020 Annual Data Report: Lung. *Am J Transplant* 2022; 22(S2): 438-518.

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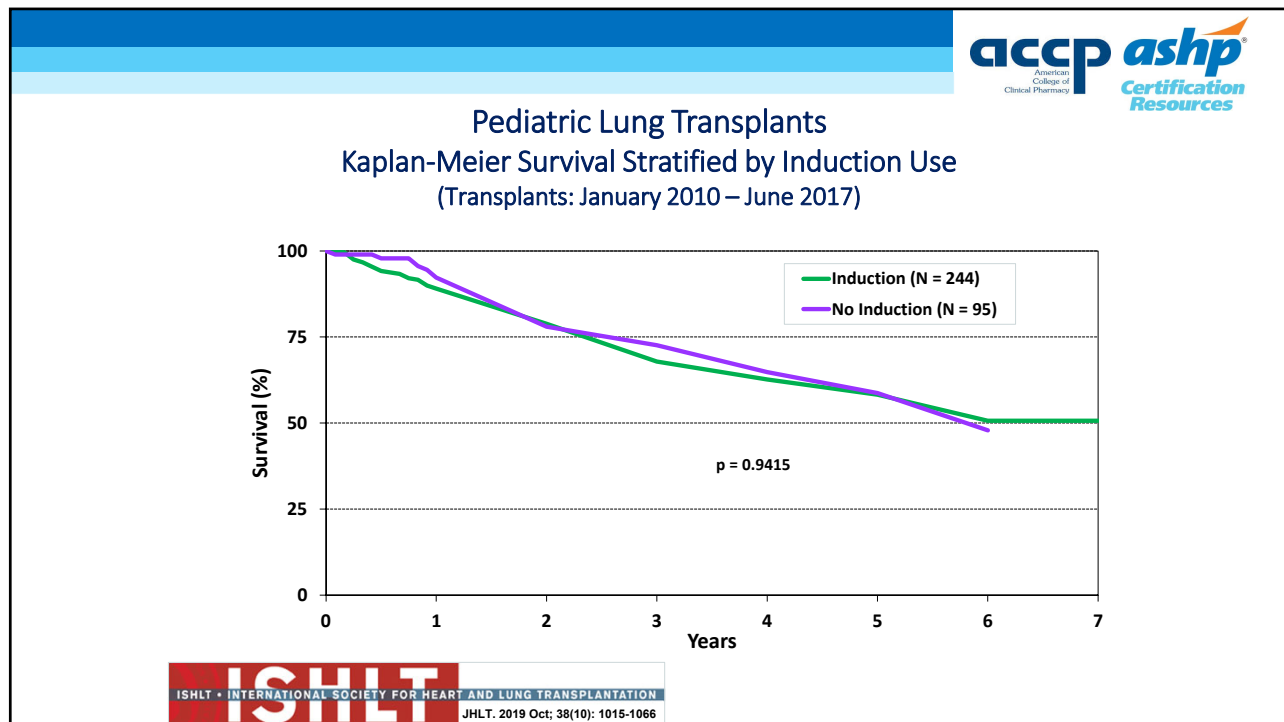
Pediatric Lung Transplants Induction Immunosuppression (Transplants: January 2010 – June 2018)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
JHLT. 2019 Oct; 38(10): 1015-1066

Analysis is limited to patients who were alive at the time of discharge.

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Question 1: Which of the following statements is true regarding immunosuppressive strategies?

- Induction immunosuppression is uncommon in both adult and pediatric lung transplantation.
- The evidence supporting induction immunosuppression in lung transplantation is robust and supportive.
- Polyclonal antibodies are the predominant strategy for induction immunosuppression in adult lung transplantation.
- IL-2 receptor antagonists are the predominant strategy for induction immunosuppression in adult lung transplantation.

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Question 1: Which of the following statements is true regarding immunosuppressive strategies?

- Induction immunosuppression is uncommon in both adult and pediatric lung transplantation.
- The evidence supporting induction immunosuppression in lung transplantation is robust and supportive.
- Polyclonal antibodies are the predominant strategy for induction immunosuppression in adult lung transplantation.
- IL-2 receptor antagonists are the predominant strategy for induction immunosuppression in adult lung transplantation.

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Maintenance Immunosuppression in Lung Transplantation

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RCTs: tacrolimus vs cyclosporine

Study	N	Concomitant Immunosuppression	Results
Griffith 1994	74	methypred x24h + aza; pred added if >2 AR in 6 weeks	AR at 6 mos: 89% vs 100%; p<0.05 AR episodes per 100 patient days: 1.2 vs 2; p<0.05 pred added in 66% vs 94%; p<0.0001
Keenan 1995	133	aza + prednisone	AR at 2 yrs: 86% vs 88%; p=ns AR episodes per 100 patient days: 0.85 vs 1.09; p=0.07 obliterative bronchiolitis at 2 yrs: 22% vs 38%; p=0.025
Zuckermann 2003	74	rATG + MMF + pred	AR at 1 yr: 54% vs 49%; p=ns AR episodes per 100 patient days: 0.22 vs 0.32; p=0.097
Hachem 2007	90	basilix + aza + pred aza -> sirol if rejection	≥A2 AR at 1 yr: 36% vs 61%; p=0.04 composite of AR/BO/BOS at 1 yr: 55% vs 85%, p=0.002
Treede 2012	249	MMF + pred	AR at 3 yrs: 67% vs 75%; p=0.118 ≥grade 1 BOS at 3 yrs: 12% vs 21%; p=0.037

Griffith BP, et al. *Transplantation* 1994; 57: 848. Keenan RJ, et al. *Ann Thorac Surg* 1995; 60: 580.

Zuckermann A, et al. *J Thorac Cardiovasc Surg* 2003; 125: 891. Hachem RR, et al. *JHLT* 2007; 26: 1012. Treede H, et al. *JHLT* 2012; 31: 797.

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RCTs: mycophenolate vs azathioprine

Study	N	Concomitant Immunos	Results
Palmer 2001	81	cyclo + pred	≥A2 AR at 6 mos: 63% vs 58%; p=0.82 drug discontinuation at 6 mos: 30% vs 16%; p=0.19
McNeil 2006	320	rATG + cyclo + pred	≥A2 AR at 3 yrs: 57% vs 60%; p=ns BOS at 3 yrs: 27% vs 25%; p=0.7 drug discontinuation at 3 yrs: 47% vs 60%; p=0.02
Speich 2010	156	nonrandomized! MMF, n=108; aza, n=48 cyclo + pred	AR 38% vs 73% ; p<0.001 BOS grade 1 at 5 yrs: 41% vs 35%; p=ns Survival at 5 yrs: 79% vs 64%; p=0.062

Palmer SM, et al. *Transplantation* 2001; 71: 1772.

McNeil K, et al. *Transplantation* 2006; 81: 998.

Speich R, et al. *Pulm Pharmacol Ther* 2010; 23: 445.

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RCTs: mTOR-I to reduce CNI

Study	N	Study Intervention	Results
NOCTET	92 lung recipients	At >1 year post-transplant: add everolimus and reduce CNI by 30-70% vs control	eGFR after 1 yr: +2.3 vs -1.3; p=0.07 eGFR after 2 yrs: +2.5 vs -3.5; p=0.02 eGFR after 5 yrs: -5 vs -5.4; p=0.916 AEs were more frequent in everolimus arm
Gottlieb et al	130 lung recipients	At 3-18 mos post-transplant: 1) Quadruple low CNI everol (tr 3-5) + CNI (tacro tr 3-5 or cyclo tr 25-75) + AM + pred 2) Control CNI (tacro tr >5 or cyclo tr >100) + AM + pred	eGFR after 1 yr: 65 vs 55; p<0.001 BPAR, CLAD, death similar Safety endpoints similar

Gullestad L, et al. *Transpl Int* 2016; 29: 819.
 Gottlieb J, et al. *Am J Transplant* 2019; 19: 1759.

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RCTs: mTOR-I to replace antimetabolite

Study	N	Study Intervention	Results
Bhorade 2011	181	basilix + tacro + aza + pred At 3 mos post-transplant: switch aza to sirolimus vs control	≥A2 AR at 1 yr: 18% vs 24%; p=0.09 BOS at 3 yrs: 30% vs 22%; p=0.48 VTE events in 17% vs 3%; p<0.01 drug discontinuation at 3 yrs: 64% vs 49%; p<0.05
Snell 2006	213	cyclo + aza + pred At ≥3 months post-transplant: switch aza to everolimus vs control	FEV1/graft loss/death at 1 yr: 22% vs 34%; p=0.046 FEV1/graft loss/death at 2 yrs: 44% vs 45%; p=ns BPAR at 2 yrs: 20% vs 34%; p=0.018 drug-related adverse events: 80% vs 57%; p<0.001
Glanville 2015	164	cyclo + MMF + pred At ≥1 month post-transplant: switch MMF to everolimus vs control	AR at 3 yrs: 41% vs 54%; p=ns ≥grade 1 BOS at 3 yrs: 29% vs 30%; p=0.95 Patient survival at 3 yrs: 76% vs 84%; p=0.19 More VTE w/everol. More leukop/diarrh/CMV w/MMF.
Streuber 2016	190	cyclo + MMF + pred At ≥1 month post-transplant: switch to everol + reduced dose cyclo vs control	BOS at 2 yrs: 21% vs 14%; p=0.25 Patient survival at 2 yrs: 89% vs 87%; p=0.664

Bhorade S, et al. *Am J Respir Crit Care Med* 2011; 183:379. Snell GI, et al. *Am J Transplant* 2006; 6: 169.
 Glanville AR, et al. *JHLT* 2015; 34: 16. Streuber M, et al. *Am J Transplant* 2016; 16: 3171.

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Belatacept in Lung Transplantation

- Timofte et al = 8 cases
 - Median 585 (139-1414) days post-transplant, with 6 months of follow-up
 - Belatacept 10 mg/kg IV on days 0, 4, 14, 28, then q28 days with reduced CNI (tacro trough 2-6 ng/ml; cyclo trough 75-100 ng/ml)
 - 1 (13%) BPAR; eGFR improved
- Iasella et al = 11 cases
 - Median 492 (range 8-3276) days post-transplant, with median 136 days of follow-up
 - Belatacept 10 mg/kg on days 1, 5, 15, 29, 45, 59 then 5 mg/kg q28 days, OR Belatacept 5 mg/kg q2 weeks x6 then 5 mg/kg q28 days
 - 5 (45%) BPAR and 2 (18%) progression of CLAD; eGFR improved
- Benninger et al = 85 cases **abstract only**
 - Median 293 (IQR 148-611) days post-transplant, with median 311 (IQR 182-465) days of follow-up
 - Belatacept dosing not provided
 - Stable graft function; stable renal function; 33% stopped infusion, a majority due to infections complications

Timofte I, et al. *Transpl Int* 2016; 29: 453-63.

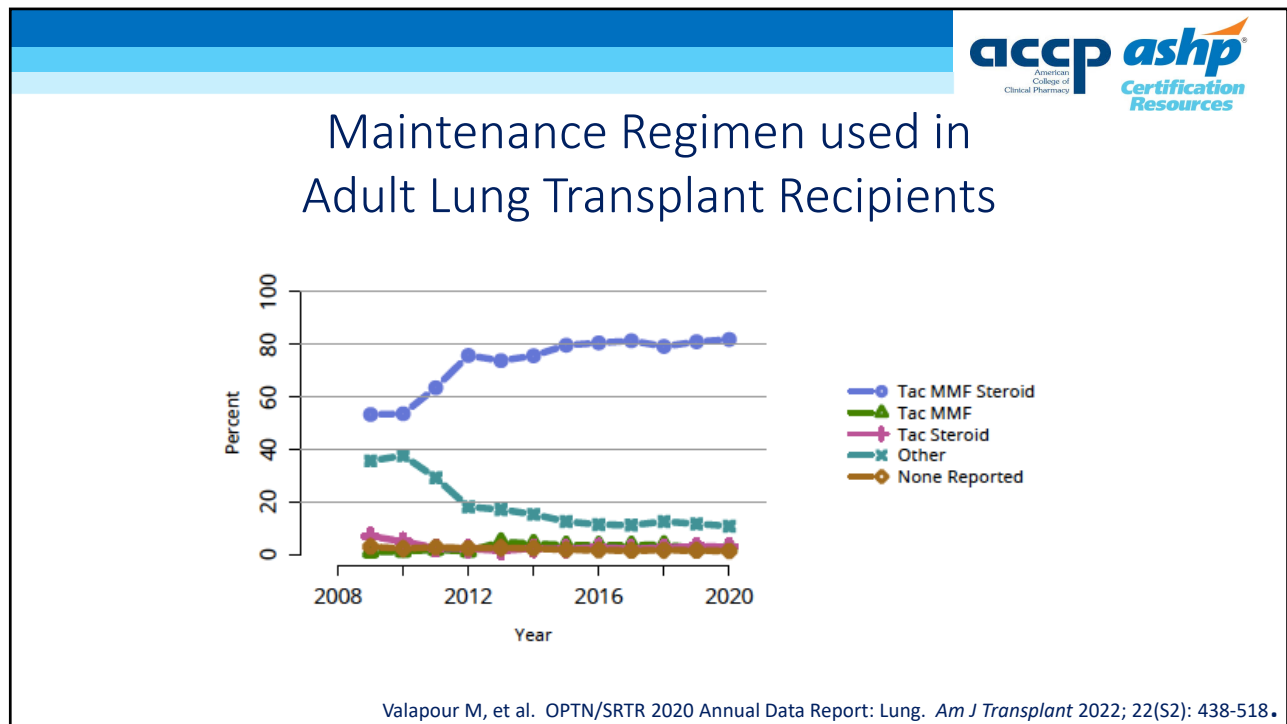
Iasella CJ, et al. *Transplantation* 2018; 102: 171.

Benninger L, et al. *JHLT* 2021; 40(4S): S77-78.

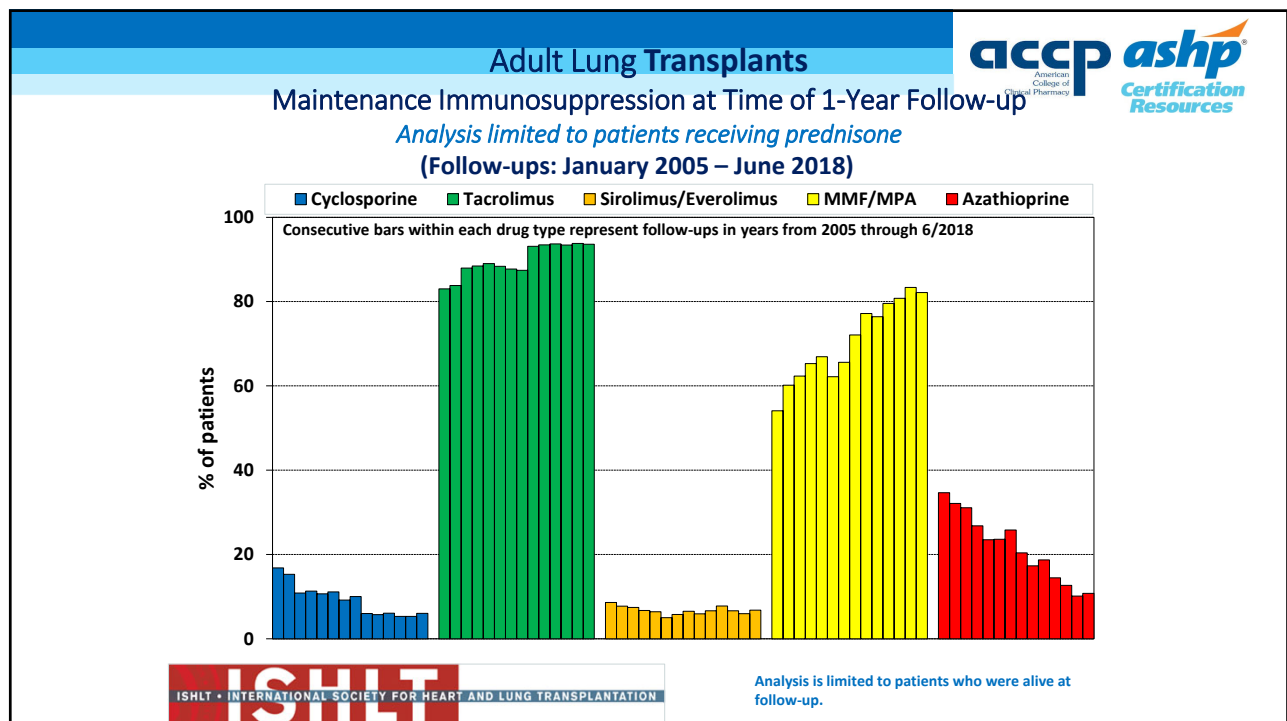
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National and International Trends in Immunosuppressive Choices

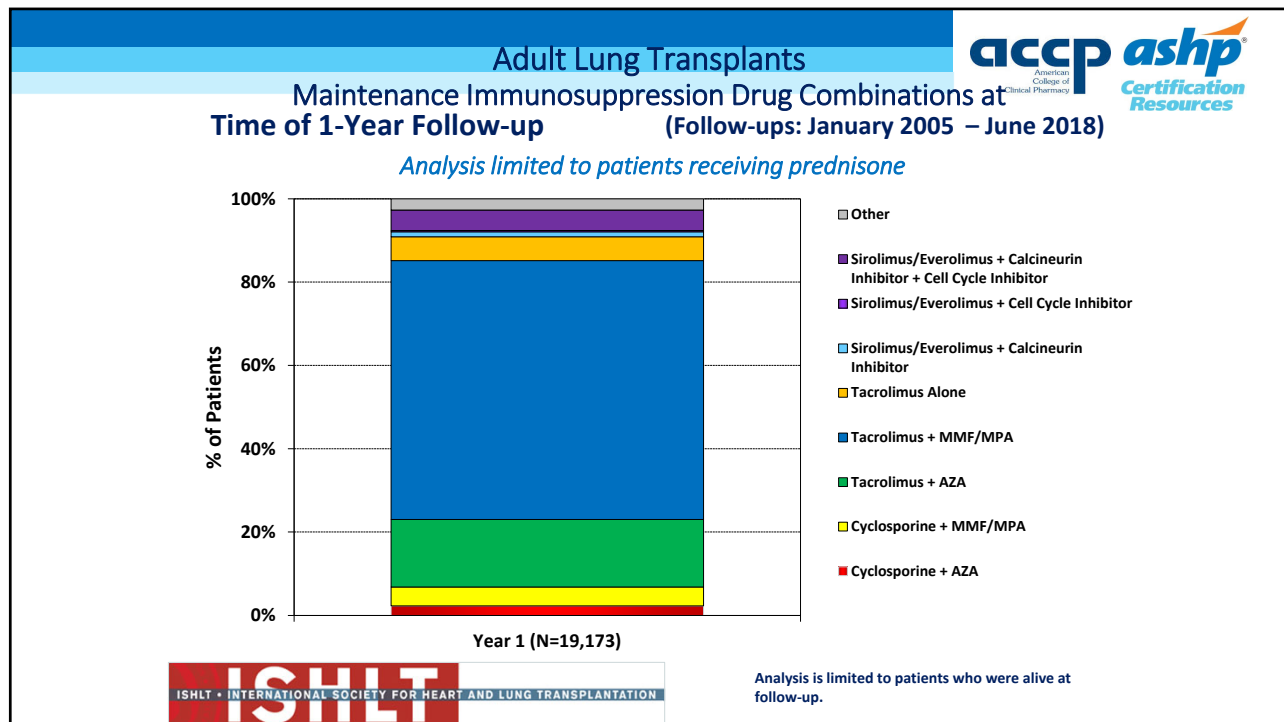
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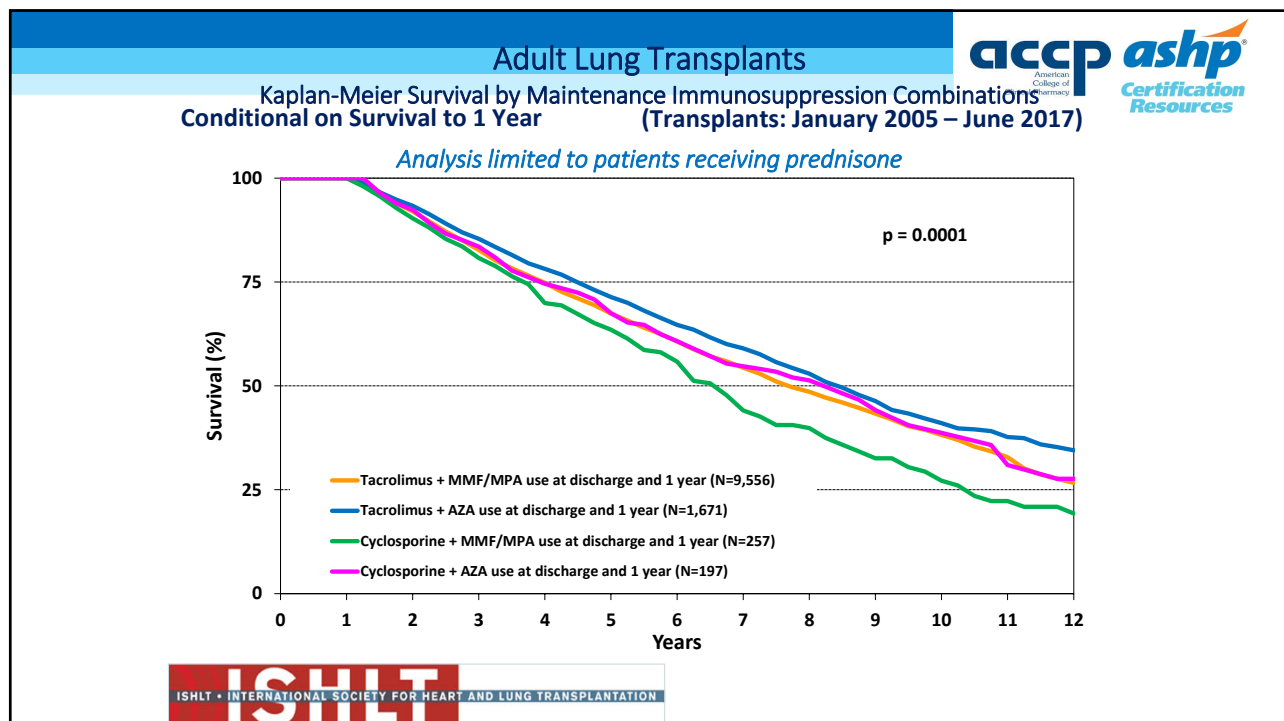
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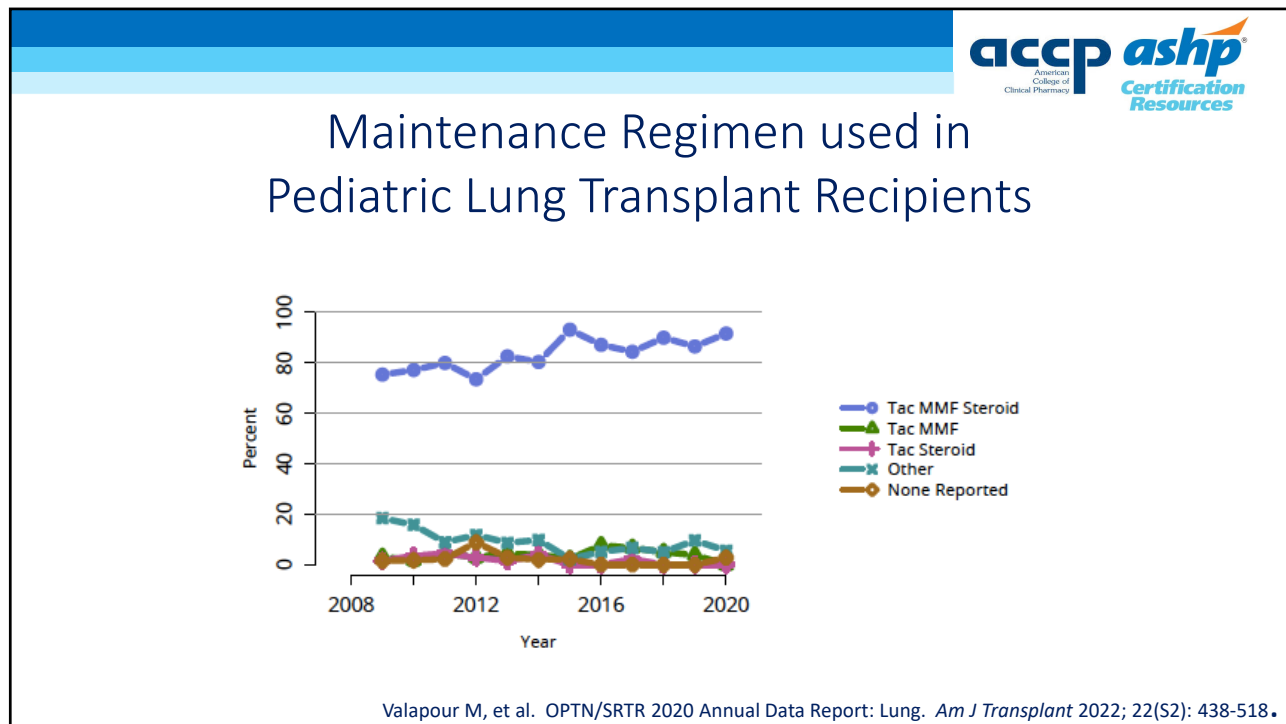
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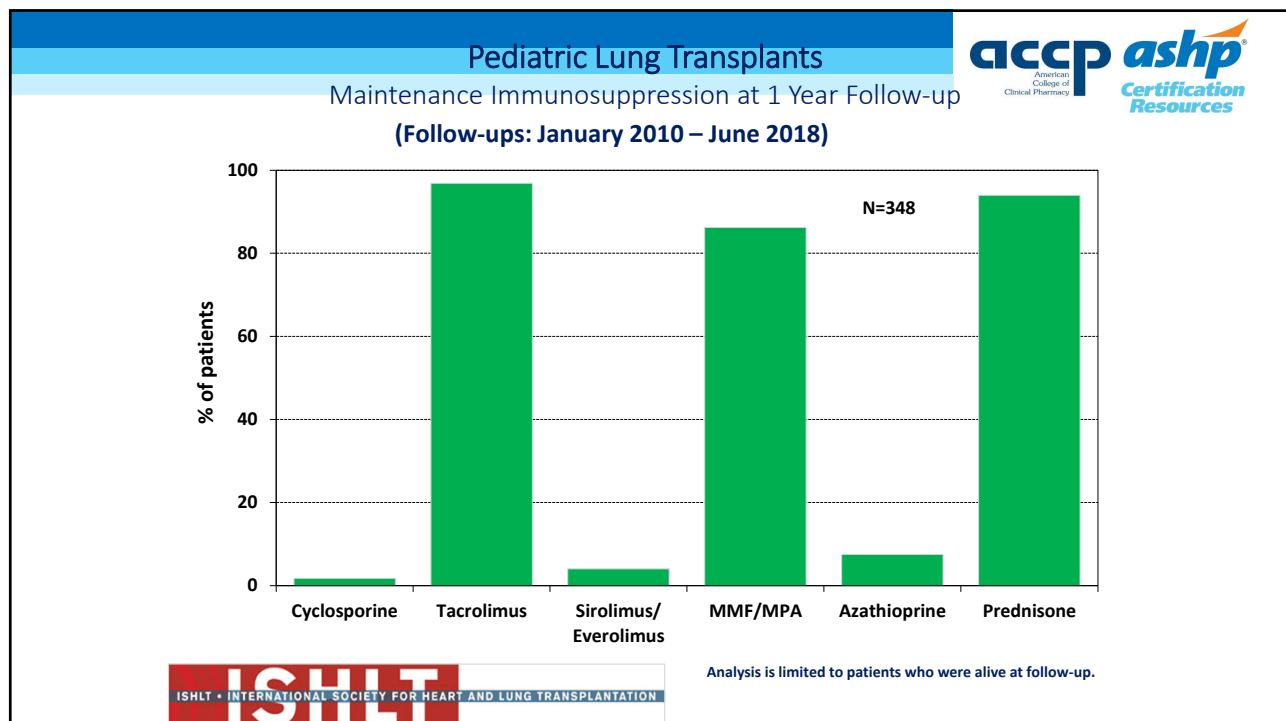
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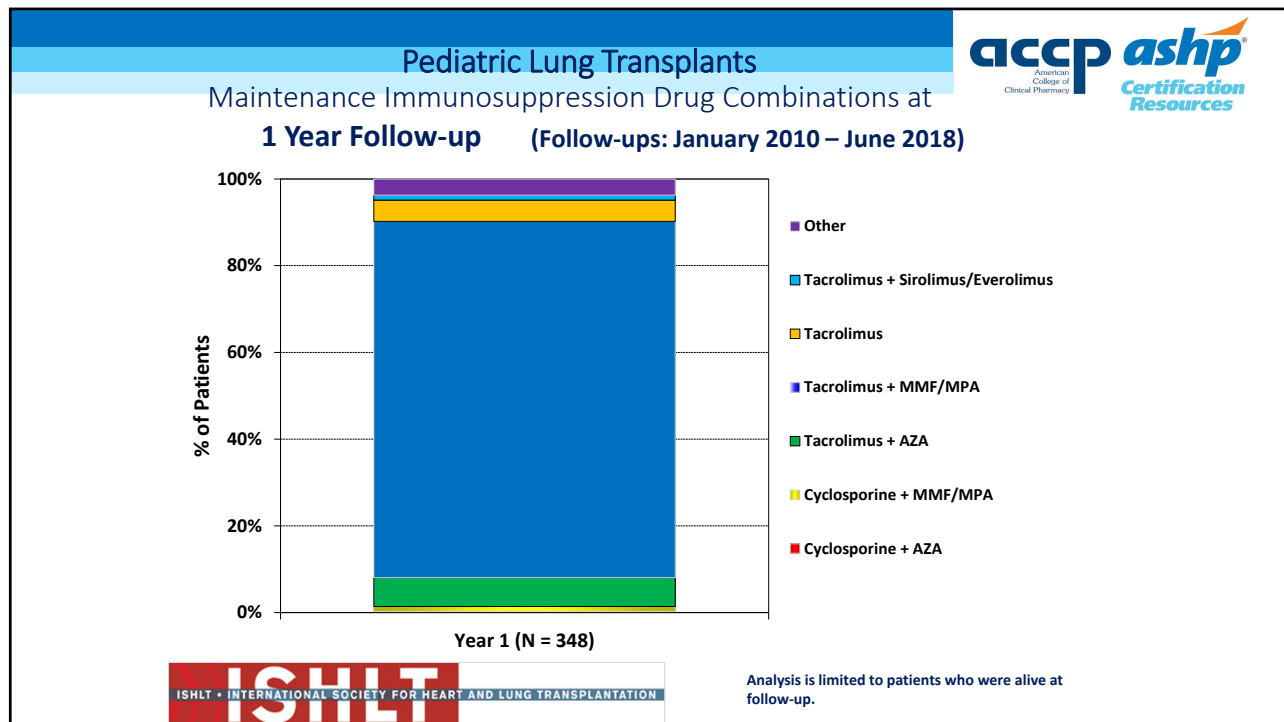
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Question 2:

Which of the following is the most commonly used immunosuppressive regimen in adult lung transplantation?

- No induction with tacrolimus + mycophenolate + prednisone maintenance
- Basiliximab induction with tacrolimus + mycophenolate + prednisone maintenance
- Basiliximab induction with tacrolimus + azathioprine + prednisone maintenance
- Basiliximab induction with tacrolimus + mycophenolate maintenance. Use prednisone short-term post-transplant only.

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Question 2:

Which of the following is the most commonly used immunosuppressive regimen in adult lung transplantation?

- No induction with tacrolimus + mycophenolate + prednisone maintenance
- **Basiliximab induction with tacrolimus + mycophenolate + prednisone maintenance**
- Basiliximab induction with tacrolimus + azathioprine + prednisone maintenance
- Basiliximab induction with tacrolimus + mycophenolate maintenance. Use prednisone short-term post-transplant only.

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Question 3:

Which of the following is true?

- Tacrolimus has demonstrated superior immunologic outcomes versus cyclosporine.
- Mycophenolate has demonstrated superior immunologic outcomes versus azathioprine.
- Everolimus use immediately after lung transplantation offers improved renal function without drug-related risk.
- No randomized controlled trials have evaluated the efficacy of maintenance immunosuppression in lung transplantation.

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Question 3: Which of the following is true?

- Tacrolimus has demonstrated superior immunologic outcomes versus cyclosporine.
- Mycophenolate has demonstrated superior immunologic outcomes versus azathioprine.
- Everolimus use immediately after lung transplantation offers improved renal function without drug-related risk.
- No randomized controlled trials have evaluated the efficacy of maintenance immunosuppression in lung transplantation.

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Key Takeaways

- There is a paucity of data on immunosuppression in lung transplantation.
- No induction is an option; need timely introduction of maintenance immunosuppression.
- IL-2 RAs offer a questionable benefit without risk.
- Polyclonal antibodies offer a questionable benefit with risk.
- Triple-drug immunosuppression is important.
- Tacrolimus offers improved rejection and BOS rates vs cyclosporine.
- Do not use mTOR-I early post-transplant, due to wound healing impairment.
- Belatacept can be used with caution; watch dosing and consider keeping CNI.

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Maintenance of Immunosuppression Part Two - Lung Transplantation

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