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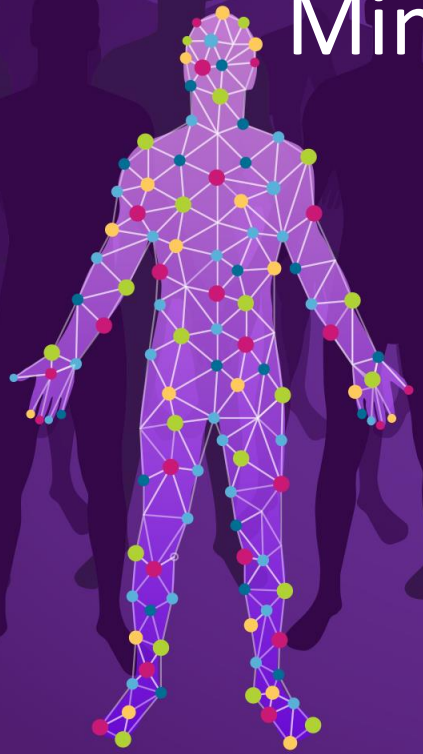
Renal Sparing Protocols – Minimizing Risk and Maximizing Benefit in Individual Patients



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CEOT CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Disclosure

- No COI or Financial Disclosures
- None of the drugs I will be discussing have FDA approval for use in lung transplantation

Learning Objectives

1. Recognize the incidence of renal insufficiency after lung transplantation and the role of CNI in nephrotoxicity seen after lung transplantation.
2. Understand the potential role of certain induction agents as renal sparing therapies in the later period after lung transplantation.
3. Recognizing the role of mTOR Inhibitors as part of a renal sparing protocol
4. Understanding the utility and limitations of belatacept as a renal sparing agent

Introduction

- **The advent of calcineurin inhibitors (CNI) revolutionized solid organ transplantation**
  - **Mitigating the risk of ACR**
  - **Side effects present**

- **CNI most common cause of nephrotoxicity**
  - Hypotension, aggressive diuresis, pre tx renal insufficiency, diabetes , hyperlipidemia, hypertension

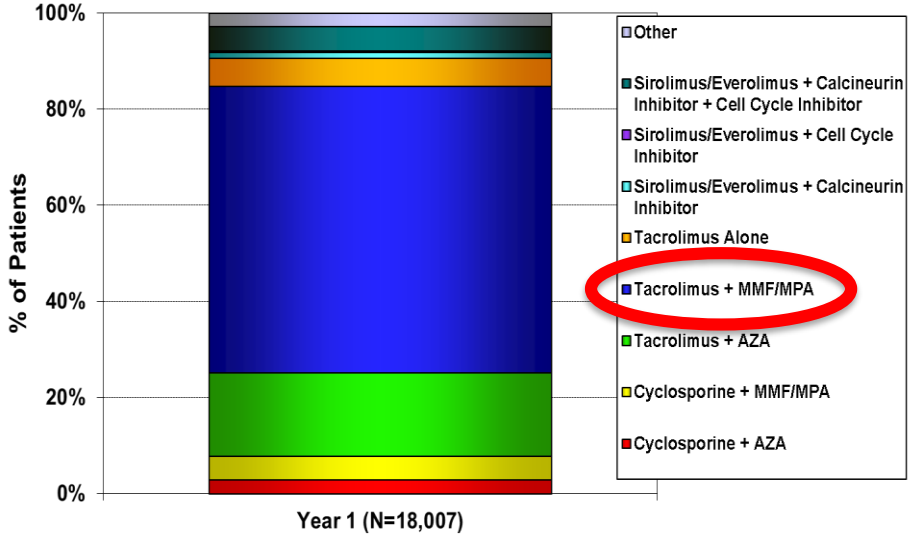
- **Nephrotoxicity is most common long term medical complication after lung transplantation**
  - 6 months post transplant, 91% lung tx patients have decline renal function
  - Incidence renal dysfyunction 26% 1 yr post tx, 38% 5 yrs post tx
  - Chronic renal failure (Cr > 2.5 mg/dl) occurs at incidence of 6.8% 1 yr post tx, 11% 5 yrs post tx
  - RRT long term 1.7% pts 1 yr , 3.2% pts 5 yrs

- **Renal failure adversely impacts mortality**
  - 4-5 fold increase in the risk of death

Transplant Proc 2017;49:2153-2160.
Transplant Proc 2105;47:1966-1971.
JHLT 2012;31:244-251.
J Crit Care 2014;29:1028-1034.

Background

- Reality immunosuppression in lung transplantation is slow to evolve
- Increasing need for renal sparing immunosuppression
  - Older recipients
  - Sicker patients
- Several promising strategies and possibly new agents may address this issue
- Presently, CNIs continue to have a pivotal role in the immunosuppressive regimen



JHLT. 2018 Oct; 37(10): 1155-1206

CNI

- CNI nephrotoxicity can present as acute or chronic or overlap
  - AKI – dose dependent, hemodynamically mediated , reversible with dose reduction
  - CKI – insidious, progressive irreversible renal interstitial fibrosis leading to impairment in function
- Tacrolimus (TAC) use advanced over the decades, target troughs have been reduced, but CKD still an issue
- Limited pharmacokinetic studies investigating TAC therapeutic dose monitoring (TDM)
- Do not accurately predict TAC exposure
  - Current TDM based on trough concentrations extrapolated from kidney and liver models
  - Limited prospective evidence to guide practice and inform the direct relationship between trough concentrations and efficacy and toxicity

Transplantation 2016;100:1723-1731.
JHLT 2007;25:1431-1435.

TAC ER

- **Extended release (ER) tacrolimus – once daily administration**
- **No formulation approved for use in USA**
  - Narrow peak trough differences (unlike with BID dosing)
  - Improve adherence
  - With increasing time in therapeutic range (TTR) may reduce adverse effect exposure
- Only 2 studies evaluating TAC ER in lung transplant recipients
  - studies are not outcomes based, only pharmacokinetic in nature assessing the potential for use in stable lung transplant recipients.
  - Potential for use in CF patients , gastroparesis , tx patients with early CKD
- McCormack et al –speculated once a day dosing in renal transplants improved renal function

Curr Transplant Reports 2018;5:212-219
Drugs 2014;74:2053-2064.

Induction Therapy

- **Induction agents**
  - Administered during **early** perioperative period to suppress T cell immune response
    - Mitigate acute rejection early
    - Delay in early utilization of CNI or lower the maintenance immunosuppressive therapy
  - Role for induction therapies given **later** as renal sparing agents ?
    - CLAD/BOS type + CKD
    - CF patient gastroparesis + CKD Stage III

Basiliximab (BAS) Renal Sparing Early and Later?

- **Mainly used for early perioperative induction**
- Case reports describing **later** post tx use as renal sparing agent
- Ross et al. N=9 (2013 +/- 2051 days post tx, mean age 64.3 +/- 11.3 yrs) with Stage III B – V CKD per MDRD Formula (III B n=2 , IV n=6 V n=1) ,
  - n=7 CLAD prior to study
  - Received BAS monthly 20 mg > 6months
  - Allowed lowering of TAC levels (2-4 ng/ml)
  - Monitored GFR 1,3,6,12 months and FEV1
  - **Conclusion:** During BSX treatment, eGFR Mean Slope: +0.747 +/- 0.467 (CI: +0.359) mL/min/1.73m2
    No progression in CKD to ESRD
    No change in FEV1 or development of DSA
    1 pt CARV /BOS II at 3 m , 1 pt died sepsis

-Demonstrated monthly BAS administration allowed for reduction in CNI therapies well tolerated with improved eGFR over 6-12 months

Ross JD et al. JHLT 2017;36:S.411

Alemtuzumab (ALE) Induction Combined With Maintenance Immunosuppression

- **Single center retrospective analysis n=446(2007-2015)**
  - Kidney function, infectious complications, rejection , and overall survival
- **3 Pt Groups No induction (n=165) , r-ATG (n=50) , alemtuzumab (n=231) followed by triple drug therapy (TAC (target level depending induction agent used) + MMF + steroids)**

Table 1. Maintenance immunosuppression protocol.

	Calcineurin Inhibitors				Aprednisolone mg/kg		Anti-proliferative	
	No induction /ATG		Alemtuzumab		No induction /ATG	Alemtuzumab	No induction /ATG	Alemtuzumab
	CyA ng/ml	Tacrolimus ng/ml	CyA ng/ml	Tacrolimus ng/ml			MMF	
0–3 months	300–350	15–18	200	10–12	0.3	0.2	1–1.5g twice a day	-
3–6 months		13–15		8–10	0.2	0.15	1–1.5g twice a day	-
6–12 months	250–300	10–12	150	6–8	0.15	0.1	1–1.5g twice a day	-
12–24 months	200	8–10	150	5–7	5 mg/d	5 mg/d	1–1.5g twice a day	1–1.5gtwice a day
>24 months	100–200	8	100–150	5			1–1.5g twice a day	

PLOS ONE 2019;14:e0210443
https//doi.org10.137/journal.pone.0210443 January 15, 2019

Results :Vienna Experience

- Pretx kidney function same in all groups
- **ALE cohort** had lower incidence of kidney insufficiency (GFR <60 ml/min) during all periods in the followup vs NI or rATG cohort
- Similar results were seen when eGFR calculated using MDRD formula
- All 3 cohorts showed a decrease of eGFR following transplant *

PLOS ONE 2019;14:e0210443
https//doi.org10.137/journal.pone.0210443 January 15, 2019

Long Term Kidney Function Preserved

Alemtuzumab cohort had a lower incidence of kidney insufficiency during follow up for 3 yrs , higher eGFR

This is first large study that demonstrated significant differences in renal function between different induction regimens

Table 4. Median serum creatinine level during long-term follow-up.

	Induction therapy			*p-value*
	No	ATG	Alemtuzumab	
Before Tx	0.8 (0.15–8)	0.79 (0.42–1.49)	0.78 (0.23–3.2)	0.102
3 months	1.22 (0.44–3.79)	1.1 (0.54–2.1)	1.07 (0.25–3.75)	**<0.001**
6 months	1.42 (0.62–6.32)	1.28 (0.7–2.7)	1.22 (0.3–3.1)	**<0.001**
1 year	1.52 (0.63–5.74)	1.48 (0.56–3.2)	1.28 (0.47–4.2)	**<0.001**
2 years	1.48 (0.7–5.27)	1.48 (0.8–3)	1.24 (0.63–3.36)	**<0.001**
3 years	1.56 (0.7–7.38)	1.45 (0.92–4.9)	1.31 (0.37–3.05)	**0.015**
≥ 4 years	1.46 (0.6–7.65)	1.37 (0.85–6.89)	1.30 (0.80–3.97)	0.875

LOS ONE 2019;14:e0210443
https//doi.org10.137/journal.pone.0210443 January 15, 2019

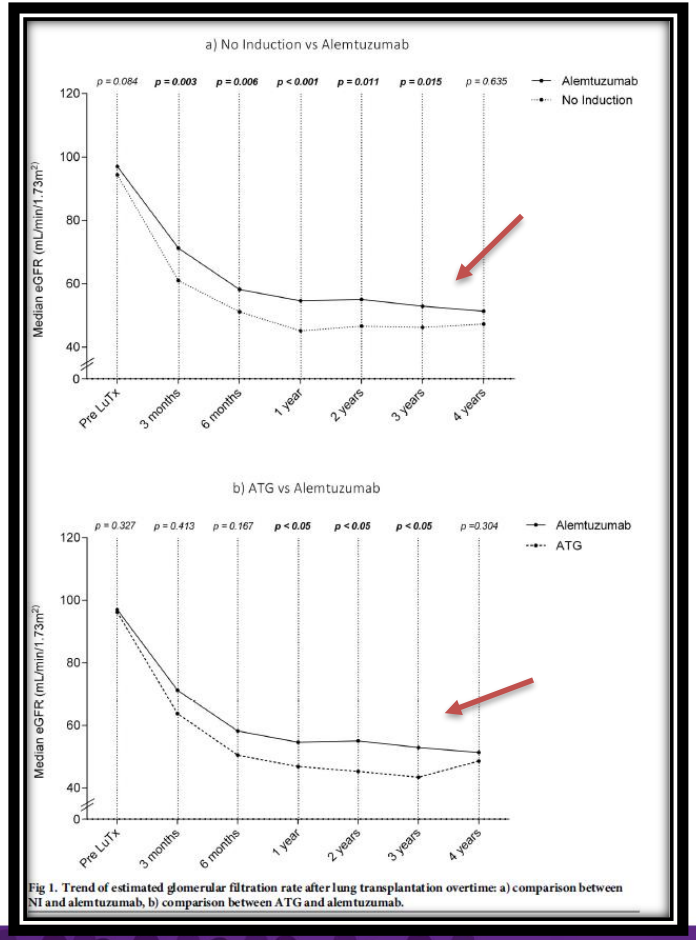
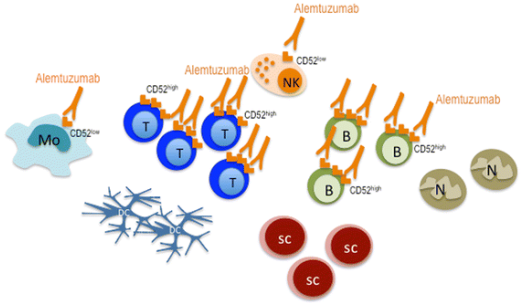


Fig 1. Trend of estimated glomerular filtration rate after lung transplantation overtime: a) comparison between NI and alemtuzumab, b) comparison between ATG and alemtuzumab.

LOS ONE 2019;14:e0210443
https//doi.org10.137/journal.pone.0210443 January 15, 2019

Other Results



- Incidence of infection lowest in ALE cohort
- Reversed after 1 yr NI lowest infection rate
- No difference in incidence of CMV, aspergillus and malignancies
- 1 yr Freedom from ACR highest in ALE cohort 97.7%, NI 83%, 91% ATG cohort
- 5 yr Freedom from CLAD rates highest ATG cohort 84.7%, NI 50.6%, 72.4% ALE cohort
- 1 yr and 5 yr survival rates highest for ALE cohort 87.3% and 77% (77.9% and 62.9% NI , 85.4% and 70.7% ATG cohort)

LOS ONE 2019;14:e0210443
https//doi.org10.137/journal.pone.0210443 January 15, 2019

Mammalian Targets of Rapamycin (mTOR)

- Sirolimus and everolimus
  - “non nephrotoxic “ CNI replacement
- mTOR important modulator of renal disease
- mTOR inhibitors shown to prevent renal graft dysfunction by reducing glomerular hypertrophy, proinflammatory/ profibrotic cytokine production, interstitial inflammation, and fibroblast production
- Synergistic effect using lower CNI doses + mTOR
  - Preservation of renal function
  - No compromising of immunosuppression
  - Risk of worsening proteinuria (majority of patients mild < 0.3 g/24hrs) but in baseline proteinuria > 0.15 g/24 hrs + significant reduced renal function → risk for nephrotic range proteinuria

Transplant Rev 2013;27:97-107
Transplantation 2016;100:2558-2568.

Combination Therapy : Renal Sparing Advantage

- Peddi et al reviewed 21 studies (2 RCT n =108 lung Tx pts) used immunosuppressive regimens that incorporate an mTOR inhibitor with TAC minimization therapy
  - Efficacy evaluated in terms of graft survival and renal function
- Conclusion: combination of mTOR + CNI had good efficacy and preservation of renal function compared to standard CNI alone
  - no changes in graft survival or rejection rates observed
  - CMV and malignancy rates low
  - Significant adverse effects seen including dyslipidemia, hypertension, proteinuria , NODM and wound healing issue in the combination group.

Transplant Rev 2013;27:97-107.

Everolimus + Reduced CNI Dosing

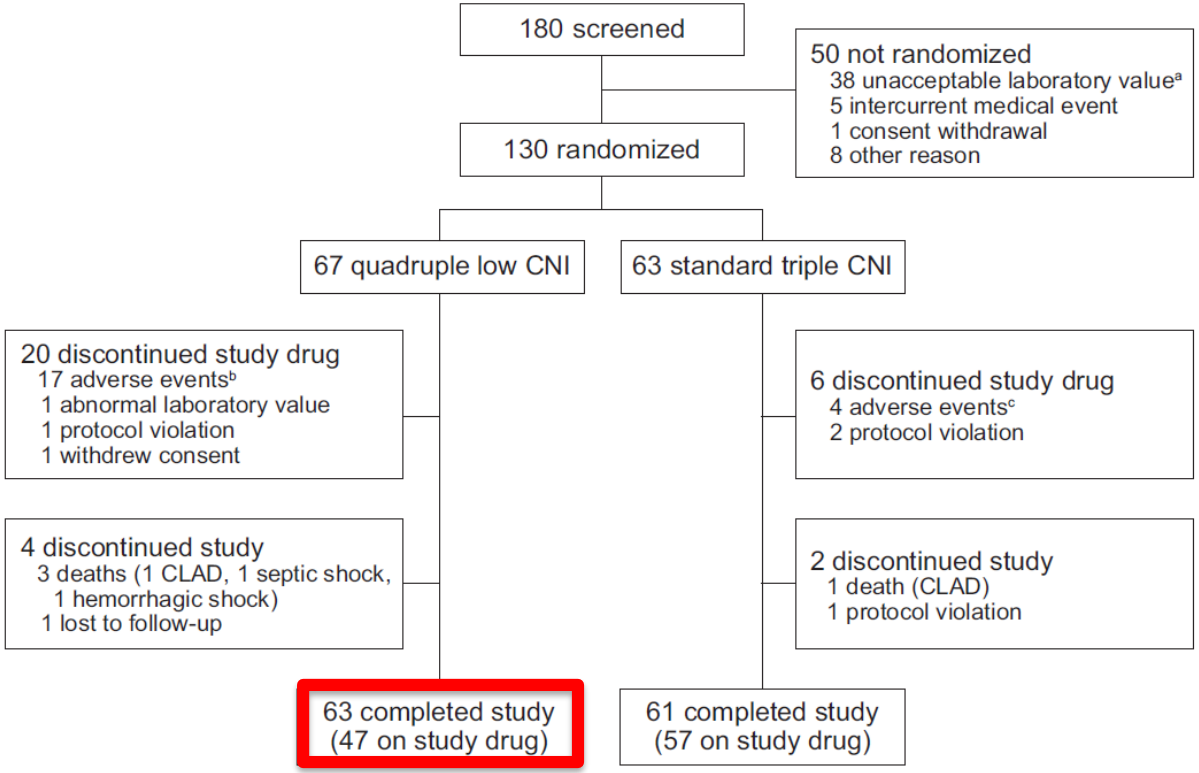
- **3 RCT Lung Transplantation – everolimus + low dose CNI therapy**
  - 2 RCT early everolimus with reduced CNI levels
    - **De novo use** of everolimus and lower CNIs did not impact post transplant renal deterioration
    - Did not specify criteria for renal function at study entry
  - 1 RCT (heart and lung tx) add on everolimus + low dose CNI **later** post transplant (NOCTET trial) > 1yr post tx
    - Enrolled mean time 52 months (? Time to development of irreversible kidney damage may enrolling earlier may be better?)
    - Moderate improvement in renal function observed after 1 and 2 yrs
    - Mean change in eGFR from baseline to 1 yr 2.3ml/min everolimus cohort and -1.3ml/min in controls (p<=0.07)
    - At last follow up > 5 yrs post randomization no between group differences and similar decline in GFR
    - High rate of pneumonia month 12 33.3% everolimus vs 9.5% control group

JHLT 2015;34:16-25.
Am J Transplant 2016;16:3171-3180.
Transplantation 2010 ;90:1581-1589.

A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation

- **4EVERLUNG** – Efficacy of Everolimus in Combination with Specific Standard Immunosuppressive Regimen in Lung Transplant Recipients
- Prospective RCT 8 sites Germany (2012-2017)- Novartis Funding
- Aim – Everolimus + low CNI dose in **Quadruple Regimen** is superior to standard triple therapy with CNI in terms of renal function
  - Unique : early initiation randomized at 3-18 months (average 10.8 m)
    impaired renal dysfunction (mild- mod eGFR > 50-90 ml/min per 1.73 m_2)
    open label study

Am J Transplant 2019:00:1-11.



[a]20 abnormal eGFR, 14 low eGFR, 4 leukopenia
[b]4 transplant rejection, 3 leukopenia, 10 other
[c]1 transplant rejection/pulmonary function decline, 2 hematological abnormality, 1 worsening of general condition

FIGURE 2 CONSORT diagram. CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; CONSORT, Consolidated Standards of Reporting Trials; eGFR, estimated glomerular filtration rate

Am J Transplant 2019:00:1-11.

4EVERLUNG: ? For Early RI and Early Post Transplant

- Marked benefit seen subpopulation pts eGFR 40-60 ml/min per 1.73m2→ 65 ml/min per 1.73m2 **(mild to moderate dysfunction)**
- Early enrollment **10.8 m** – window to minimize the time to dependent development of irreversible CNI nephrotoxity
- Everolimus target lower (3-8 ng/ml) compared to other earlier trials
- No signals of overimmunosuppression noted (ie infection) in the quadruple therapy group
- Discontinuation rate lower 29% vs 35-55% in other trials
- Potential benefit : Early initiation of patients with early CKD

Am J Transplant 2019:00:1-11.

Belatacept (BELA)

- Approved for use in kidney transplant to replace CNI
- BENEFIT study – demonstrated higher mean GFR, graft, and patient survival compared to CSA
- Lung transplant case reports and series
  - Timofte et al. retrospective review n=8 with acute and chronic kidney disease refractory to lowering CNI or change to SRL initiation received BELA for 6 months
  - Older cohort > 65 yrs old
  - BELA initiated and CNI was withheld or reduced (median 3 doses)
  - No change in FEV1 seen or ACR episodes
  - 2 pts stable GFR, 5 pts improved GFR (mean GFR 24 ml/min/1.73m2 → 28 ml/min/ 1.73 m2 (*p=0.10*) at one month and improved up to 6 months and baseline mean Cr 3.1 to 1.7 *(p=0.05*) 1 month
  - 2 out of 3 pts IHD no longer needed IHD

Am J Transplant 2010;10:535-456
Transpl Int;2016:29:453-463.

Belatacept (BELA)

- Iasella et al. single center retrospective study in n=11 converted to BELA alone
  - All pts received induction with BAS or ALE and initial standard triple drug therapy (CNI + MMF+ steroids)
  - Converted to BELA at discretion of physician n=4 TTP, 3= PRES, 2= recurrent ACR , 1= CLAD, 1= renal sparing
  - Mean eGFR higher post BELA cohort (32.53 vs 45.26 ml/min/ m2) *p=0.04*
  - Difficult to draw conclusions regarding efficacy of BELA

Transplantation 2018;102:171-177

Personalizing Immunosuppression

- Narrow therapeutic index the limitation
  - Inter and intra patient variability
    - Genetic polymorphisms of cytochrome p450 3A enzymes and the transport protein P-glycoprotein
    - Age, clinical status , disease states , interacting medications

Summary

- Several strengths and limitations of the potential renal sparing agents and regimens
- No definitive renal sparing regimen
  - Still need to be tailored for the individual patient for maximum benefit .
  - NO “ONE SIZE FITS ALL” APPROACH!
  - Need for carefully designed and conducted clinical trials

Thank You

From the top of Camelback Mountain