2017 CST-Astellas Canadian Transplant Fellows Symposium

Management of Renal Dysfunction in Extra Renal Transplants

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Disclosure

Jeffrey Schiff, MD

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Kidney Disease in Non-Renal Transplant Recipients

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Objectives

- Describe the incidence of kidney disease (CKD) post-transplant
- Review common causes of kidney disease in non-renal solid organ transplant patients
- Analyze results of randomized controlled trials of immunosuppression changes to preserve renal function
- Discuss the role of renal transplant in non-renal transplant patients with ESRD

Case Presentation

- 60-year-old woman
- Double lung transplant 5 years ago for emphysema
  - Excellent lung function
- Hypertension x 1 year
- Osteoporosis
- 45 pack-year smoking history, quit x 13 years
- No history of diabetes, dyslipidemia, CAD, CVA, PVD

Case Presentation

- Current medications
  - Cyclosporine, Myfortic, prednisone
  - Amlodipine 5 mg daily
  - Septra, azithromycin, calcium carbonate, vitamin D, omeprazole, domperidone, folic acid, paroxetine, buproprion, clonazepam
- No history of renal disease pre-transplant
- No urologic, renal or uremic symptoms
- No history of acute kidney injury, dialysis

Case Presentation

- O/E
  - BMI 29.1
  - BP 140/84
  - Remainder of exam unremarkable
- Labs
  - Hb 123 g/L
  - Normal electrolytes, Ca/PO4/albumin
  - Creatinine 120 µmol/L (eGFR 40 ml/min), 129-175 over last 4 years
  - 24-hr urine creatinine clearance 72 ml/min pre-transplant
  - Urinalysis negative for blood and protein

Case Presentation

- What is this woman's underlying diagnosis?
- Does she need a renal biopsy?
- Should her immunosuppression be changed in order to preserve renal function?
- What else can be done to preserve her renal function?

Renal Function Is Often Abnormal and Misestimated Pre-Transplant

- Serum creatinine often normal in patients with end-stage organ disease
  - Decreased creatinine production in cirrhosis
  - Decreased muscle mass due to malnutrition
- Effects of end-organ disease or treatments may affect renal function or renal blood flow
  - Hypotension in advanced heart failure
  - Hepatorenal syndrome
  - Diuretics, ACE-inhibitors, ARBs
  - Nephrotoxic antibiotics
- Cockroft-Gault, MDRD and CKD-EPI equations may be inaccurate
- 24-hour urine collection may not be any better

Acute Kidney Injury- Common, Deadly, and Leads to CKD

- Retrospective study of 359 liver transplants in 300 patients
- Identified patients with acute renal injury (2x increase in creatinine) and acute renal failure (3x increase or dialysis)
- ARI (11.1%) and ARF (25.7%) were common post-transplant

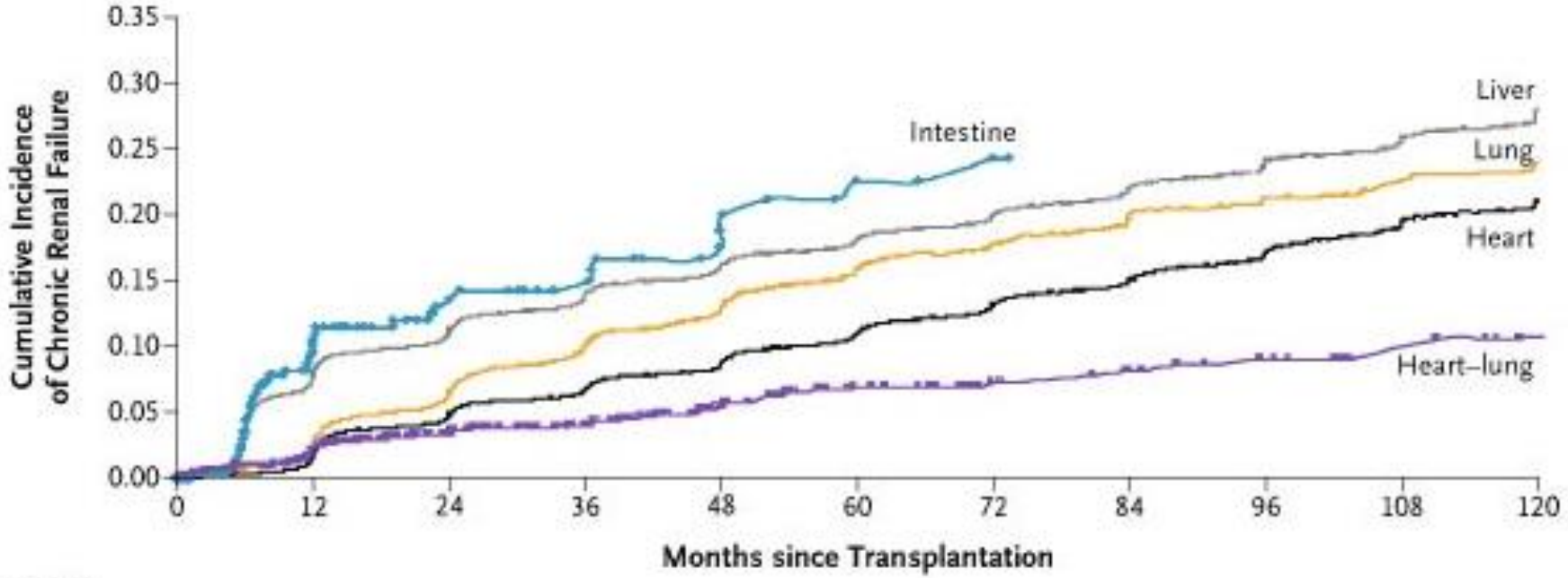
Table 5: Cox regression multivariate analysis of the effect of risk factors on 30-day and 1-year patient survival

30-day patient survival	p	HR	95% CI
Fulminant hepatic failure	0.65		
Inotrope use	0.16		
Rejection	0.01	0.1	0.0–0.6
Hemorrhage	0.21		
ARF	0.03	2.8	1.1–6.9
1-year patient survival	**p**	**HR**	**95% CI**
Diabetes mellitus	0.02	1.9	1.1–3.3
Pre-OLT creatinine	0.19		
Primary biliary cirrhosis	0.41		
Inotrope use	0.17		
Cytomegalovirus infection / disease	0.03	4.9	1.1–19.3
Rejection	0.89		
ARF	0.001	2.6	1.5–4.5

ARF: acute renal failure; OLT: orthotopic liver transplantation; HR: hazard ratio; CI: confidence interval.

O'Riordan et al Am J Transpl 2007;7:168

CKD is Common Post-Transplant



No. at Risk											
Heart–lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

Stage 4 and 5 CKD only

Ojo et al. N Engl J Med 2003;349:931

Risk Factors

Pre-Tx GFR

Post-OP ARF

PreTx dialysis

Cyclosporine

Hepatitis C

HTN, DM

Year of Tx

Ojo et al NEJM 2003;349:931

Table 3. Risk Factors Associated with Chronic Renal Failure in Recipients of Nonrenal Organ Transplants.*

Variable	Overall Relative Risk (95% CI)	P Value	Relative Risks in Subgroups of Recipients		
			Liver Transplants	Heart and Heart–Lung Transplants	Lung Transplants
Age (per 10-year increment)	1.36 (1.34–1.38)	<0.001	1.29	1.56	1.40
Pretransplantation glomerular filtration rate					
≥90 ml/min/1.73 m²	1.00 (reference group)		1.00	1.00	1.00
60–89 ml/min/1.73 m²	1.38 (1.30–1.46)	<0.001	1.54	1.16†	1.00†
30–59 ml/min/1.73 m²	2.25 (2.12–2.39)	<0.001	2.54	1.92	1.00†
≤29 ml/min/1.73 m²	3.41 (3.15–3.70)	<0.001	3.78	2.82	1.42†
Missing or unknown	1.33 (1.21–1.46)	<0.001	1.25	1.29	1.13†
Postoperative acute renal failure‡	2.13 (1.99–2.27)	<0.001	2.11	3.03	4.56
Dialysis treatment before transplantation	1.46 (1.27–1.68)	<0.001	1.45	1.25†	—§
Male sex	0.74 (0.71–0.77)	<0.001	0.71	0.78	0.68
Race					
White	1.00 (reference group)		1.00	1.00	1.00
Black	1.02 (0.95–1.10)	0.57	1.01†	1.05†	0.91†
Asian	0.77 (0.66–0.89)	<0.001	0.79	0.86†	0.32†
Other	0.73 (0.63–0.85)	<0.001	0.76	0.58	1.34†
Calcineurin-inhibitor treatment during initial hospitalization					
Tacrolimus	1.00 (reference group)		1.00	1.00	1.00
Cyclosporine	1.24 (1.17–1.30)	<0.001	1.25	0.98†	1.09†
Missing or unknown	0.87 (0.80–0.95)	<0.001	0.63	1.04†	1.10†
Sirolimus treatment during initial hospitalization					
No	1.00 (reference group)		1.00	1.00	1.00
Yes	1.19 (0.94–1.52)	0.16	1.21†	1.82†	0.36†
Hepatitis B	1.06 (0.96–1.18)	0.25	1.04†	1.41†	0.66†
Hepatitis C	1.15 (1.08–1.23)	<0.001	1.22	1.34	1.07†
Hypertension before transplantation	1.18 (1.10–1.26)	<0.001	1.04†	1.24	1.26
Diabetes mellitus before transplantation	1.42 (1.33–1.51)	<0.001	1.39	1.51	1.53
Year of transplantation					
1998–2000	1.00 (reference group)		1.00	1.00	1.00
1994–1997	1.08 (1.02–1.14)	0.008	1.23	0.80	0.84
1990–1993	1.31 (1.15–1.48)	<0.001	1.52	0.92†	0.62

Liver Program

MDRD eGFR Range		Dialysis	Neph	Neph + Dialysis	Grand Total
< 15	5	1	16	3	25
15 - 29	22		29	1	52
30 - 59	399	3	112	2	516
60 - 89	547	2	28		577
>= 90	209		2		211
Grand Total	**1182**	**6**	**187**	**6**	**1381**

Lung Program

MDRD eGFR Range		Dialysis	Neph	Neph + Dialysis	Grand Total
< 15	5		11	2	18
15 - 29	43		41	2	86
30 - 59	282	4	91	2	379
60 - 89	155	1	14		170
>= 90	60		2		62
Grand Total	**545**	**5**	**159**	**6**	**715**

Source: OTTR

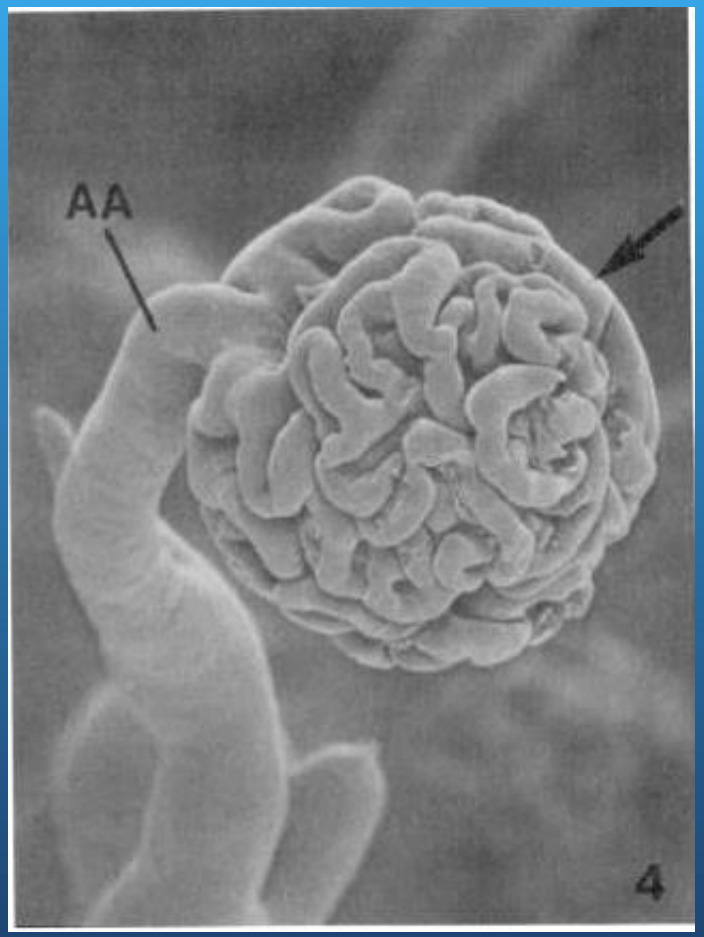
Causes of Chronic Kidney Disease Post-Transplant

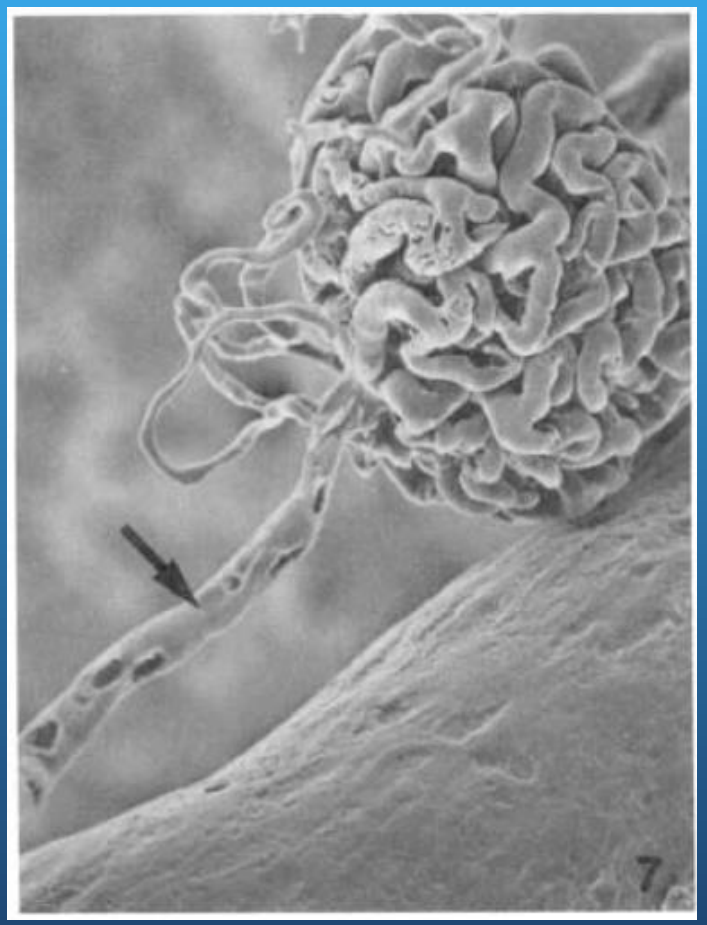
- Calcineurin inhibitor nephrotoxicity
- Previous acute kidney injury/acute tubular necrosis
- Pre- or post-transplant
  - Hypertension
  - Diabetes
- Atherosclerotic renal disease
- Primary or secondary glomerulonephritis
  - HBV- or HCV-related
  - De novo
- Rare: thrombotic microangiopathy, polyomavirus nephropathy

Nephrotoxicity of Calcineurin Inhibitors

- Acute reversible decrease in GFR
  - Afferent arteriolar vasoconstriction
- Chronic progressive or non-progressive decrease in GFR
  - Hypertension
  - Bland urinary sediment
  - Proteinuria uncommon
  - Interstitial fibrosis and tubular atrophy
  - Arteriolar hyalinosis
- Acute or chronic thrombotic microangiopathy – rare

Acute CnI Toxicity

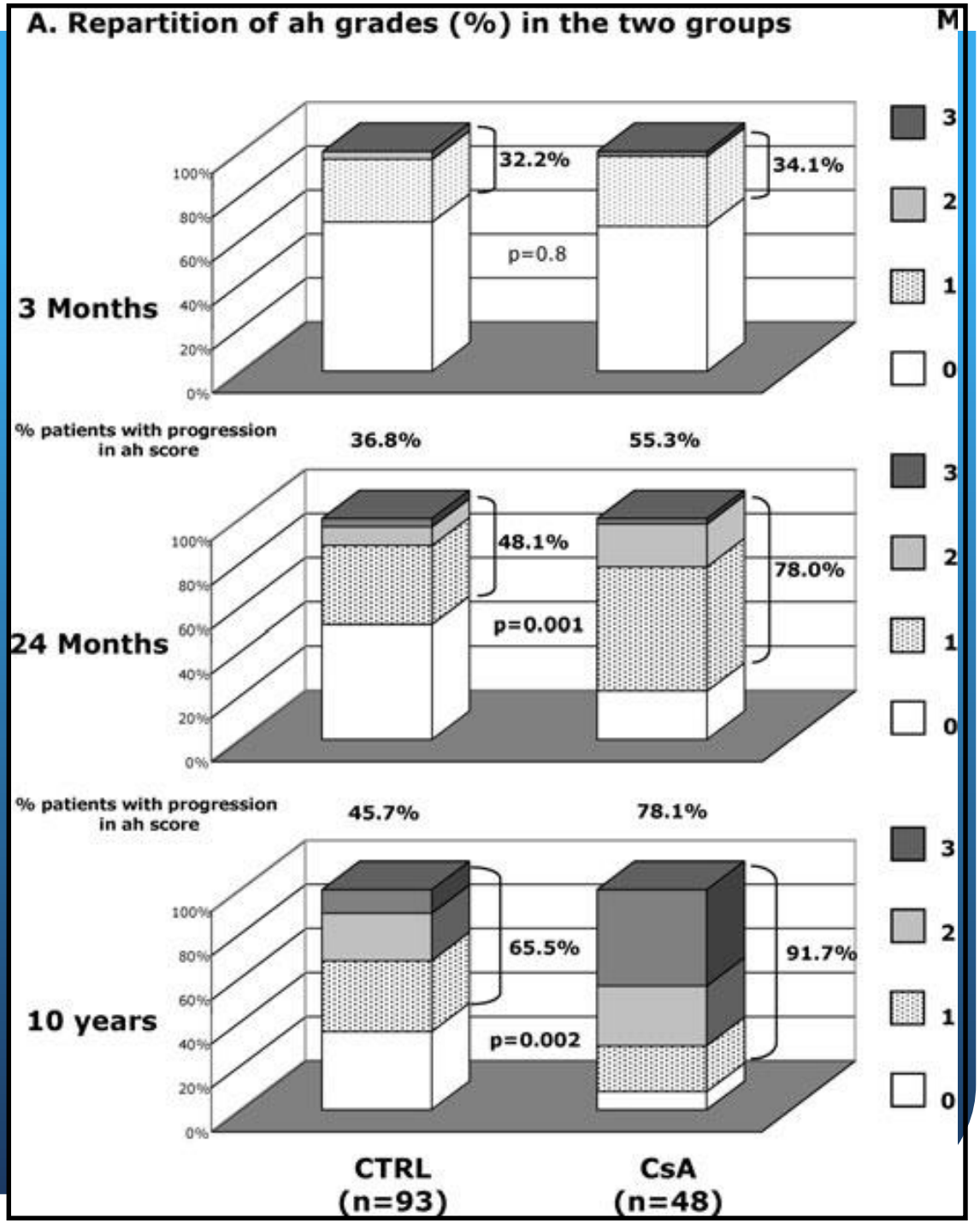




English et al, Transplantation 1984;44:135

What Defines CnI Toxicity?

- Protocol biopsy study in RTx recipients
- Development of all chronic changes of CnI toxicity in patients, regardless of IS



Snanoudj et al, Am J Transpl 2011;11:2635

Chronic CnI Toxicity Post-Nonrenal Transplant

- Allows for “cleaner” assessment of CnI effect
  - Not confounded by rejection, ischemia-reperfusion injury, recurrent disease, etc.
- Most reports of histologic changes are biased
  - Single-center
  - For-cause biopsies
  - Most patients deviate from typical natural history

Common Histologic Findings

- Non-specific
  - Interstitial fibrosis and tubular atrophy
  - Arteriolar hyalinosis
- Possibly specific
  - Focal segmental glomerulosclerosis
- Specific
  - Diabetic nephropathy
  - Glomerulonephritis (e.g. MPGN, membranous nephropathy, IgA)
  - Thrombotic microangiopathy
  - Polyomavirus nephropathy

When to Biopsy?

- Active urinary sediment
- Proteinuria
- Rapid change in renal function
- Uncertainty about diagnosis

Immunosuppressive Strategies to Preserve Renal Function

- Delayed calcineurin inhibitor introduction
- Calcineurin inhibitor substitution
- Calcineurin inhibitor reduction
- Calcineurin inhibitor avoidance

Delayed CnI Introduction

- Open-label multi-center RCT
- Patients randomized to:
  - Tacrolimus, MMF, steroids
  - Daclizumab, tacrolimus delayed to day 5, MMF, steroids
- Target tacrolimus levels 10-20 ng/mL for first 4 weeks, then 5-15 ng/mL
- Primary endpoint percentage of patients with serum creatinine >130 µmol/L at 6 months post-transplant
- Primary endpoint reached in delayed tacrolimus group 22.4% vs. 29.7% in standard group (p=NS)

Calmus et al, Transplantation 2010;89:1504

CnI Substitution

- Replace calcineurin inhibitor with sirolimus or MPA
- Key issues:
  - Renal function at time of substitution
  - Timing of conversion
  - Medication side effects
  - Safety – rejection, graft loss

Liver Spare The Nephron (STN) : Study Design

Inclusion

Adult patients (18 to 74 yrs)
Randomization: 30-90 days post Tx

Antibody induction and/or **steroids** administered according to individual center practice

Treated with CNI + MMF + Steroids

1:1 Randomization (N = 293)

SRL Conversion (n = 148)

MMF (1-1.5g BID)
Sirolimus (2-4 mg/day; trough 5-10ng/ml)
MEAN TIME =52 +/- 11 days

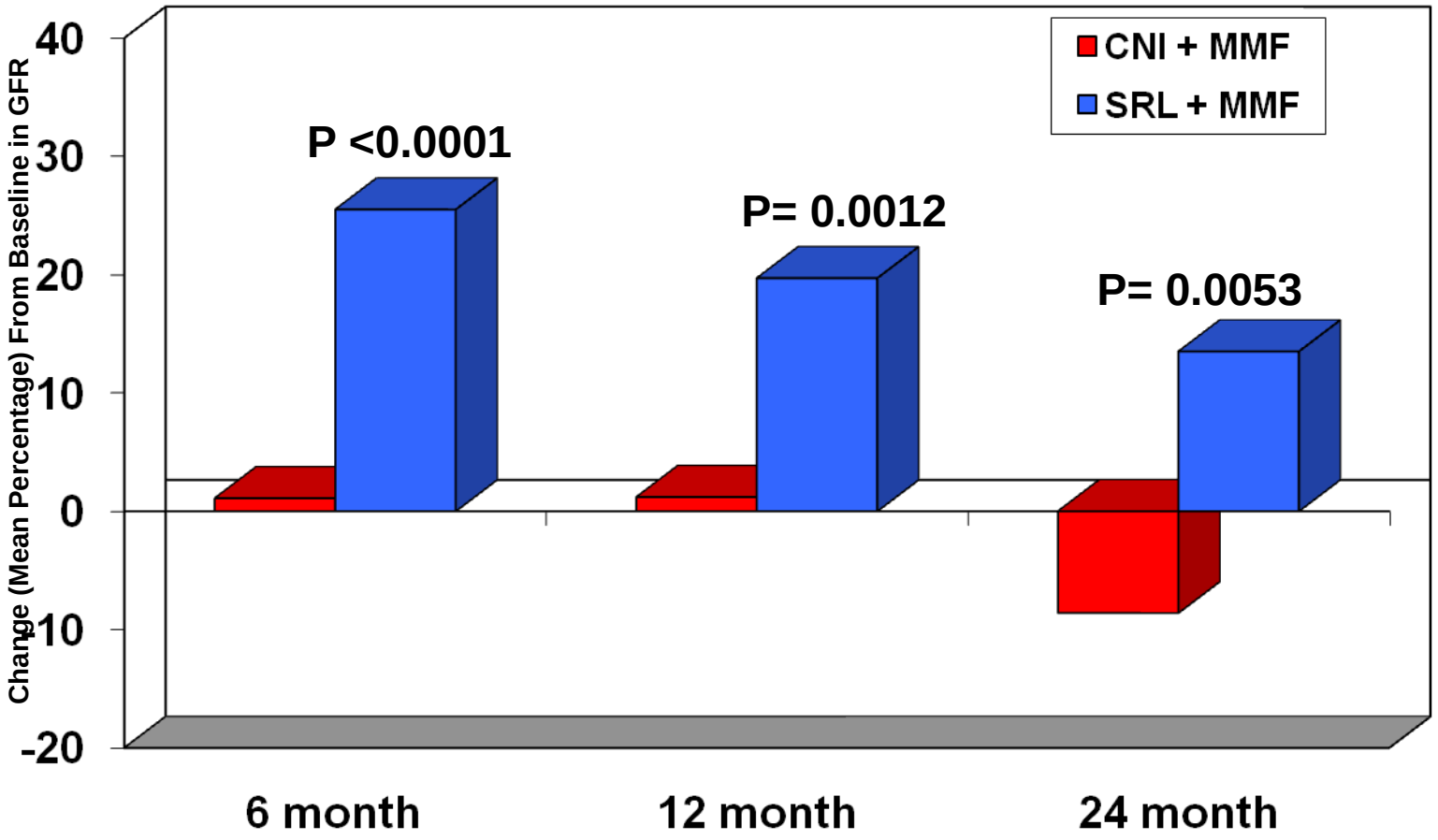
CNI Continuation (n = 145)

Tac (0.1- 0.15mg/day; trough 3-10ng/ml)
CsA (3-5 mg/kg BID; trough 100-250 ng/ml)
MEAN TIME = 50 +/- 10 days

http://clinicaltrials.gov/ct2/show/results/NCT00118742?sect=X9876015#outcome4 Accessed Nov 2011

http://www.roche-trials.com/studyResultGet.action?studyResultNumber=ML18423 Accessed Nov 2011

Liver Spare the Nephron (STN): Change From Baseline in Glomerular Filtration Rate (GFR)



http://clinicaltrials.gov/ct2/show/results/NCT00118742?sect=X9876015#outcome4 Accessed Feb 2012

http://www.roche-trials.com/studyResultGet.action?studyResultNumber=ML18423 Accessed Feb 2012

Liver Spare the Nephron (STN): Safety Endpoints

Endpoint	CNI + MMF	SRL + MMF	P value
BPAR (up to 24 mo)	6 (4.1%)	18 (12.2%)	0.0159
Graft loss (up to 24 mo)	14 (9.7%)	8 (5.4%)	0.1175
Death	10	6	
Treatment failure (to 12 mo)	55 (37.9%)	72 (48.6%)	0.0845
Patients with at least 1 SAE	65 (45%)	67 (45%)	NS
Discontinuation due to AE or infection	37 (25%)	53 (36%)	
New onset or worsening hyperlipidemia	50.0%	70.3%	0.0004
New onset or worsening diabetes mellitus	26.7%	14.2%	0.0084
New or worsening malignancy	10 (6.8%)	7 (4.7%)	NS

http://clinicaltrials.gov/ct2/show/results/NCT00118742?sect=X9876015#outcome4 Accessed Feb 2012

http://www.roche-trials.com/studyResultGet.action?studyResultNumber=ML18423 Accessed Feb 2012

Wyeth Study 313: Study Design

Inclusion

6 months to 12 yrs after liver transplantation
CNI-based immunosuppression
Anti-metabolite therapy permitted

2:1 Randomization (N = 607)

SRL Conversion (n = 393)

SRL troughs: 8-16 ng/mL
± anti-metabolite (AZA or MMF)

CNI Continuation (n = 214)

Continue CNI (CsA: 50-250; TAC 3-10)
± anti-metabolite (AZA or MMF)

Abdelmalek MF, Humar A, Stickel F, et al. Am J Transpl. 2012.

www.clinicaltrials.gov Accessed Jan 2012

Study 313 –Primary and Secondary Endpoints

Baseline to 12 Months

	SRL Conversion	CNI Continuation	P- Value
Number of Participants	393	214	
PRIMARY ENDPOINT			
Change from Baseline Adjusted Mean GFR (mL/min)	-4.45 ± 1.12	-3.07 ± 1.36	0.342
SECONDARY ENDPOINTS			
Graft Survival	367 (93.4%)	202 (94.4%)	0.356
Graft Loss	26	12	
Death	13 (3.3%)	3 (1.4%)	NS
Biopsy-Confirmed Acute Rejection	46 (11.7%)	13 (6.1%)	0.017
Serum Creatinine (µmol/L)	119.0 ± 38.9	122.4 ± 31.5	>0.05

Abdelmalek MF, Humar A, Stickel F, et al. Am J Transpl. 2012.

www.clinicaltrials.gov Accessed Jan 2012

Pfizer Study 408: Safety And Efficacy Of Conversion From CNI To SRL In Renally-Impaired Heart Transplant Recipients

Open-label, randomized, comparative, multicenter, multinational study

Adult cardiac transplant recipients; mild to moderate renal insufficiency (> 40, < 90 ml/min)
≥ 12mo, ≤ 96 mo after transplantation

1:1 Randomization (N = 116)

SRL Conversion (n = 57)

- SRL troughs: 7–15 ng/mL
- CNI discontinued by 8 weeks
- Continue MMF, MPS, or AZA
- Continue (±) corticosteroids

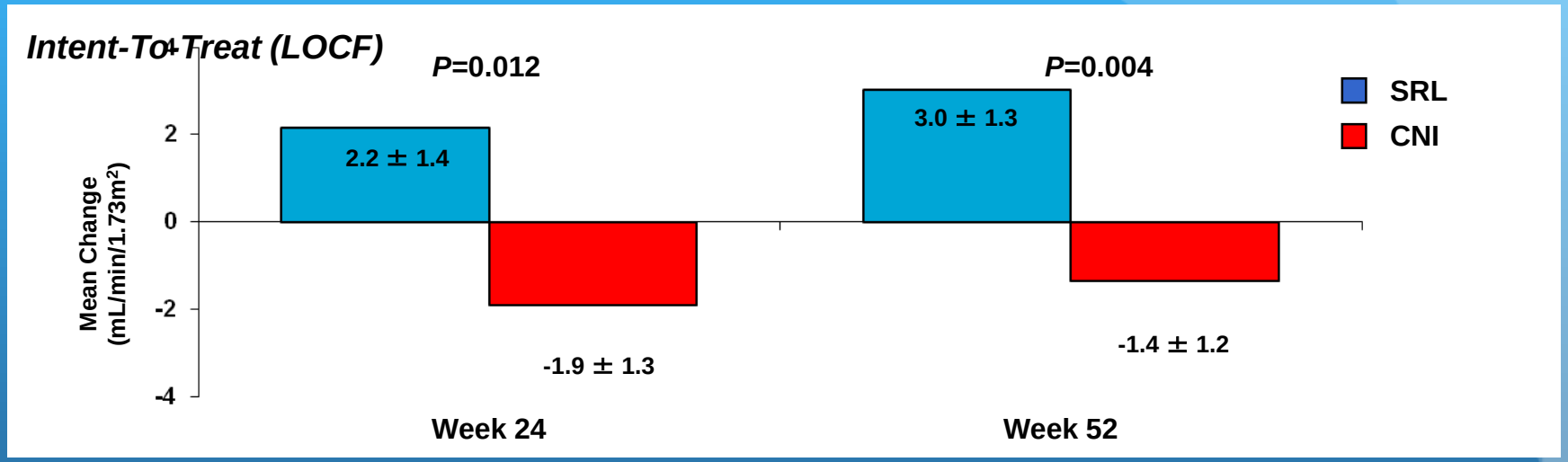
CNI Continuation (n = 59)

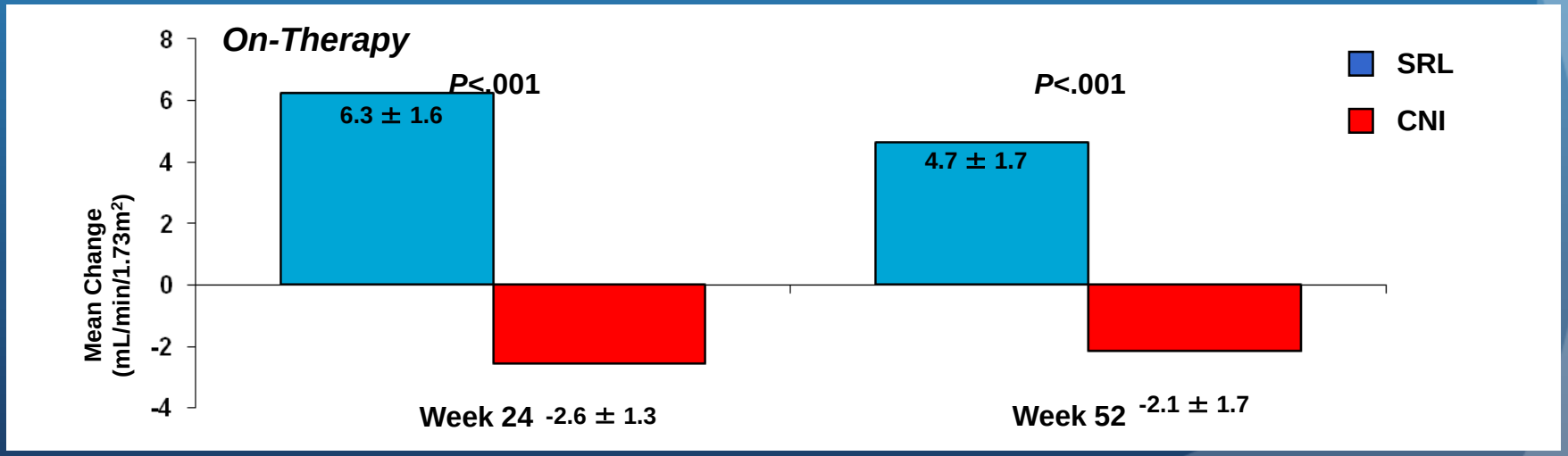
- Continue CsA (50-250 ng/mL) or TAC (3-10 ng/ml)
- Continue MMF, MPS, or AZA
- Continue (±) corticosteroids

http://www.clinicaltrials.gov NCT00369382 Accessed Feb 2012

AZA, azathioprine; CsA, cyclosporine A; MMF, mycophenolate mofetil; MPS, mycophenolate sodium

Study 408: Adjusted Mean Change (± SE) from Baseline in Estimated Creatinine Clearance





http://www.clinicaltrials.gov NCT00369382 Accessed Feb 2012

Study 408: Survival and Acute Rejection

	SRL (n=57)	CNI (n=57)
Death, n/N (%)	2/57 (3.5)	0/57 (0.0)
Biopsy-confirmed acute rejection, n/N (%)*		
Protocol mandated	7/39 (18.0)	N/A
For cause†	5/57 (8.8)	1/57 (1.8)
Site protocol†	2/11 (18.2)	0/11 (0)
Acute rejection with hemodynamic compromise, n/N (%)†,‡	1/57 (1.8)	1/57 (1.8)

*Biopsy grade 2R or higher (ISHLT 2005 criteria), rejection accompanied by hemodynamic compromise or requiring treatment

† Between-group comparison, *P*=NS.

‡Diagnosed on biopsies done for cause.

http://www.clinicaltrials.gov NCT00369382 Accessed Feb 2012

CnI Avoidance

- Use of sirolimus beginning at time of transplant
- One retrospective study showing similar outcomes of sirolimus alone compared to sirolimus with CnI and CnI alone
- No randomized controlled studies to confirm results
- Concerns of impaired wound healing, thrombocytopenia

Zaghla et al, Aliment Pharmacol Ther 2006;23:513

Non-Immunosuppressive Management of CKD

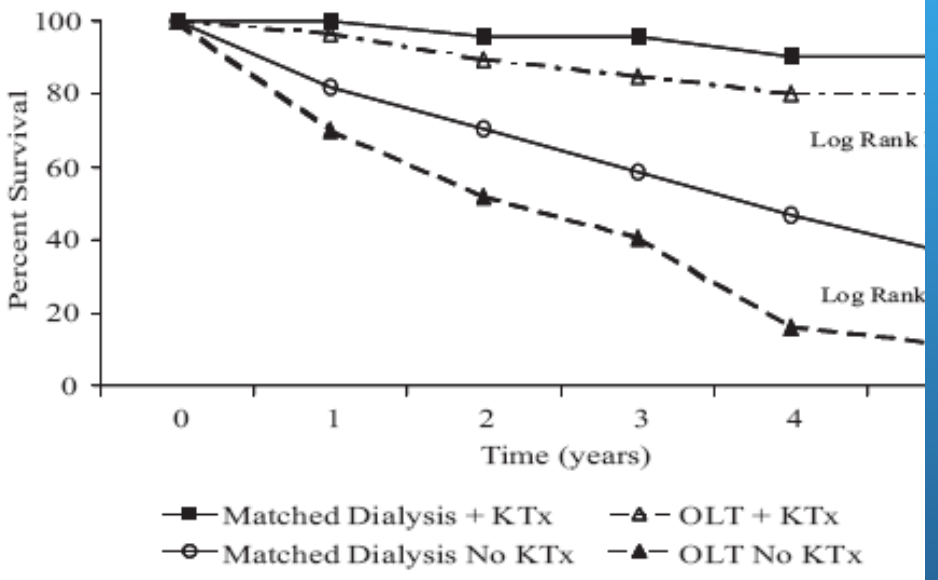
- Blood pressure control
  - Target 130/80
  - No data favouring any antihypertensive class
  - Exception: ACE-I or ARB in patients with proteinuria
- Glycemic control
  - Aggressive control in diabetic patients
- Dyslipidemia
  - Lipid targets as for patients with known CVD
- Prophylactic ASA

Non-Immunosuppressive Management of CKD

- Calcium/phosphate/PTH
  - Dietary control of phosphate
  - Calcium supplements with meals
  - Calcitriol
- Anemia
  - Iron supplementation
  - Erythropoietin/Darbepoietin
- Nutrition
  - Adequate protein intake
- Timely initiation of renal replacement therapy

Renal Transplantation in Liver Transplant Patients with ESRD

- Liver transplant patients do poorly on dialysis
- Already exposed to risks of immunosuppression
- Better outcomes overall with transplant than on dialysis
- Similar findings in heart transplantation



Effective sample size

Time (yrs)	0-1	1-2	2-3	3-4	4-5
Matched Dialysis + KTx	47	45.5	39.5	35	29
Matched Dialysis No KTx	165.5	108	71.5	45	27
OLT + KTx	29	26.5	21	17	14.5
OLT No KTx	83	46.5	27	15	3.5

Al Riyami et al, Transplantation 2008;85:1277

Should Non-renal Transplant Patients with ESRD Be Prioritized for Transplant?

Pro

- Very high mortality risk on dialysis reversed by transplantation
- Would improve outcomes of non-renal transplants
- Is often due to iatrogenic cause, i.e. calcineurin inhibitors

Con

- No priority given for patients with other high-risk comorbidities (e.g. diabetes)
- Would disadvantage patients requiring a kidney transplant alone
- May result in selection of higher-risk patients for transplant

Summary

- A common and important problem post-transplant
- Affects long-term outcomes
- Most commonly, but not always, due to calcineurin inhibitor toxicity
- Other common diseases, such as diabetes and hypertension, also contribute
- More likely to see benefit of immunosuppressive changes when done early post-transplant
- Data on best non-immunosuppressive management lacking