Chronic kidney disease in non-renal transplant patients

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Question #1

• The main cause of chronic kidney disease in heart or liver transplant recipients is:

1. Diabetic nephropathy
2. Focal segmental glomerulosclerosis
3. Calcineurin inhibitor nephrotoxicity
4. Hypertension
Question #2

• The incidence of chronic kidney disease stage 4-5 at 10 years post-heart or post-liver transplant is:

1. 5%
2. 10%
3. 15%
4. >20%
Question #3

- Heart or liver transplant recipients requiring chronic dialysis have an increased risk of death compared to other patients on chronic dialysis

1. True
2. False
Question #4

• Treatment options

  1. Delay initiation + low-dose CNI
  2. CNI dose reduction + MMF
  3. Conversion to rapamune
  4. Few randomized controlled trials
  5. All are correct
Outline

• Definition of CKD
• Etiology of CKD
• Impact of CKD on patient survival
• Prevention of CKD
• Management of CKD
  – Immunosuppresssive strategies
  – Non-immunosuppressive strategies
Definition of chronic kidney disease

Table 10. Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
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Etiology of ESRD in Nonrenal Organ Transplant Recipients

Orthotopic Heart Recipients with ESRD (n=24)¹

Orthotopic Liver Recipients with ESRD (n=45)²


*Nonrecovery from pretransplant hepatorenal syndrome.
Some cases have multiple histologic diagnosis.

Courtesy Dr. A. Ojo
Cumulative Risk of Stage 4-5 CKD in non-renal Tx recipients

n=69,321  Predictors: ARF, age, women, DM, HTN
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Outcomes in heart transplant patients with or without CrCl DROP ≥30% in the first year

Chronic Dialysis

Patient Survival

Years post heart transplantation

Time (years) 1 5 10 15 20
DROP1-12 <30%, n 165 131 88 34 14
DROP1-12 ≥30%, n 34 23 11 6 1

Logrank test p=0.004

238 HTx pts, 07/1982 – 08/2003
Survival >1-month

Outcome of heart transplant recipients on chronic dialysis: Analysis of the Canadian Organ Replacement Register

- CORR data
- 2709 HTx pts
- 105 (3.9%) on HD
- Controls: 2 HD pts

Mortality

\[ p < 0.001 \]
Survival after the initiation of dialysis

- Time elapsed between the initiation of chronic dialysis and death: 1.6–1.8 yrs (median 0.9 yrs)

**Survival Rates**

- **HTx (HD):**
  - DM: 16.1%
  - HTN: 70.3%
  - Controls: 27.3%* (80.3%)
  - *P=0.04

- CVC death
  - 45.8% vs. 31.8%
  - P<0.01

Survival Post-Kidney Tx

Time to kidney Tx after the initiation of dialysis
HTx 1.5 1.0 yrs (0.36-3.63), Controls 1.8 1.7 yrs (0.01-7.48)

Survival of liver Tx patients on chronic dialysis (CORR)

01/1981 – 12/2002, 4186 LTx pts, 2.9% on chronic dialysis

Al Riyami et al. Transplantation 2008, 15; 85(9):1277
Survival Post-Kidney Tx

![Graph showing survival rates over time for different transplant scenarios.]

**Time (years):**
- Matched Dialysis + KTx
- OLT + KTx
- Matched Dialysis No KTx
- OLT No KTx

**Effective sample size:**

<table>
<thead>
<tr>
<th>Time (yrs)</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched Dialysis + KTx</td>
<td>47</td>
<td>45.5</td>
<td>39.5</td>
<td>35</td>
<td>29</td>
<td>14.5</td>
</tr>
<tr>
<td>Matched Dialysis No KTx</td>
<td>165.5</td>
<td>108</td>
<td>71.5</td>
<td>45</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>OLT + KTx</td>
<td>29</td>
<td>26.5</td>
<td>21</td>
<td>17</td>
<td>14.5</td>
<td>7.5</td>
</tr>
<tr>
<td>OLT No KTx</td>
<td>83</td>
<td>46.5</td>
<td>27</td>
<td>15</td>
<td>3.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Log Rank P = 0.26
Log Rank P = 0.0002
Clinical vignette

- 50 yr-old man with IHD requiring HTx
- Pre-Tx eGFR 60 mL/min
- Baslixximab, Pred, Tac and MMF
- Tac 8-12 ng/mL x 3 months, then 5-8
- eGFR 48 mL/min at 3 months
- eGFR 25 mL/min at 4 years
What would you do?

1. No change and assess pre-emptive kidney Tx (eGFR <20 mL/min)
2. Reduce CNI
3. Discontinue CNI
4. Replace CNI with mTOR inhibitors
5. Other CNI replacement strategies
The boys on vacation....

Jean, where are you?
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Reduced dose tacrolimus + MMF + daclizumab in *de novo* liver transplantation

Patients with Scr >200 µmol/L were excluded

**Group A**  
Tac trough >10 ng/ml + corticosteroids  
*Regimen in drug label*

**Group B**  
Tac trough ≤8 ng/ml  
+ MMF  
+ corticosteroids

**Group C**  
Tacrolimus (≤ 8 ng/ml) delayed until day 5  
+ IL2r blockade on days 0 & 7  
  *(daclizumab 2 mg/kg & 1 mg/kg)*  
+ MMF 1g bid  
+ corticosteroids

Mayer D et al. ATC 2008
Mean change in GFR

- Standard Tac
- Reduced Tac
- Reduced, delayed Tac

Mean change in GFR from baseline to 12 months (ml/min)

* Error bars show 95% CI

Mayer D et al. ATC 2008
Acute rejection

Mayer D et al. ATC 2008

BPAR at 12 months (%)

- Standard Tac: P = 0.0054
- Reduced Tac: P = 0.1576
- Reduced, delayed Tac
Liver transplant
Spare-the-Nephron (STN)

Pre-randomization
- MMF + tacrolimus ± corticosteroids
- MMF + cyclosporine ± corticosteroids

Screening
- MMF 1.0-1.5 g bid
- CsA 100-250 ng/ml
- Tac 3-10 ng/ml

Post-randomization
- 1 year
- SRL 2-4 mg qd
  5-10 ng/ml
- MMF + tacrolimus
- MMF + sirolimus
- MMF + cyclosporine
- MMF + sirolimus

Stable
- 4 – 12 weeks
- Post-TX

Enrollment

Sher L et al, ATC 2008; Roberts J et al, ATC 2009; Teperman L et al, ATC 2009
Liver STN: Mean %GFR Increase
Baseline to Month 12

P<0.0001

19.7 ± 40.6
1.2 ± 39.9

Teperman et al. ATC 2009; Abstract #132
Liver STN: Efficacy Endpoints

Treatment failure includes BPAR, graft loss, death or loss to follow-up.

- **Treatment Failure**: 18.9% (MMF/SRL) vs 16.6% (MMF/CNI), P=0.609
- **BPAR**: 12.2% (MMF/SRL) vs 4.1% (MMF/CNI), P=0.014
- **Graft Loss**: 3.4% (MMF/SRL) vs 8.3% (MMF/CNI), P=0.072

Lipid lowering drugs:
- MMF/SRL 24%
- MMF/CNI 8%

Malignancies:
- MMF/SRL 5%
- MMF/CNI 10%

Withdrawals:
- MMF/SRL 36%
- MMF/CNI 27%

Teperman et al. ATC 2009; Abstract #132
Roberts et al. ATC 2009; Abstract #1204
Sirolimus conversion regimen vs. continued CNI in LTx

Purpose: To prevent further CNI toxicity

Table 3: Primary efficacy end point: change from baseline in Cockcroft-Gault GFR at 12 months (ITT population)¹

<table>
<thead>
<tr>
<th>Cockcroft-Gault GFR, mL/min</th>
<th>Treatment</th>
<th></th>
<th>Rank ANCOVA p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SRL conversion (n = 393)</td>
<td>CNI continuation (n = 214)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline of the adjusted mean ± SE</td>
<td>-4.45 ± 1.12</td>
<td>-3.07 ± 1.36¹</td>
<td>0.34</td>
</tr>
<tr>
<td>Maximum</td>
<td>49.67</td>
<td>45.85</td>
<td>—</td>
</tr>
<tr>
<td>75th percentile</td>
<td>6.75</td>
<td>6.00</td>
<td>—</td>
</tr>
<tr>
<td>50th percentile</td>
<td>-0.92</td>
<td>0.24</td>
<td>—</td>
</tr>
<tr>
<td>25th percentile</td>
<td>-9.98</td>
<td>-7.72</td>
<td>—</td>
</tr>
</tbody>
</table>

Sirolimus conversion regimen vs. continued CNI in LTx

- Acute rejection
  - SRL 11.7%
  - CNI 6.1% (P=0.02)

- Discontinuation
  - SRL 41.9%
  - CNI 23.3%

- Skin cancer
  - SRL 4%
  - CNI 9% (P=0.008)

No difference in pt and graft survival

Sirolimus conversion regimen vs. continued CNI in LTx

Based on these results, conversion from CNI-based to SRL-based immunosuppression did not result in renal function preservation compared with CNI continuation in maintenance LT recipients. However, given the confounding variables and limitations encountered during this trial, this strategy may still warrant further investigation.

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Immunosuppressive strategies

• Reduction of CNI dose
  – MMF ± mTor + Pred

• Discontinuation of CNI
  – MMF ± mTor + Pred
  – MMF + Pred + anti-CD25 mAb
Clinical benefit of C2 monitoring in Heart Transplantation

C2 300-600 vs. C0 100-200 ng/ml

*P. 1 vs. P. 2, P<0.00001; P. 1 vs. P.3, P=NS; **P. 3 vs. P. 2, P=0.004

Cantarovich M et al. Transplantation 1999; 68(12):1839
Long-term immunosuppression with anti-CD25 mAb in HTx pts with CKD

Cantarovich M et al. J Heart Lung Transplant 2009; 28(9):912

CD25 mAb n=17
Controls n=10

CD25 mAb: 13 10 months
Controls n=10
Long-term immunosuppression with anti-CD25 mAb in HTx pts with CKD

Change in slope of Creatinine Clearance

- CNI D/C: +0.335 mL/min/month
- Controls: -0.124 mL/min/month (P=0.03)

Cantarovich M et al. J Heart Lung Transplant 2009; 28(9):912
## CNI dose reduction and conversion
### Summary of RCT in Thoracic Tx

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Study population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| **Gleissner et al.** Am J Transplant 2006; 6(11):2750 | **Group 1:** n=19  
**Group 2:** n=20  
8.2 4.3 yrs post-HTx | **Group 1:** SRL+MMF  
**Group 2:** ↓CsA + MMF | • **Group 1:** eGFR at 6mo  
48.5 21.4 to 61.7 21.4 mL/min (P<0.001 within and between groups)  
• 16% (3 pts) D/C SRL (diarrhea, skin rash)  
• No rejection |
| **Gullestad et al.** Transplantation 2010;90:1581 | **Study group:** n=108  
**Controls:** n=127  
>1yr post-HTx & LTx | **Study group:** EVL + ↓CNI  
**Controls:** Continued on CNI | eGFR at 2 yr follow-up  
• **Study group:** ↑3.2±12.3 mL/min  
• **Controls:** ↓2.4±9.0 mL/min (P<0.001)  
**Acute rejection**  
• **Study group:** 5.6%  
• **Controls:** 3.1% (P=NS)  
**No difference in side-effects** |
Clinical benefit C2 monitoring in Liver Transplantation


*P=0.03 vs. C0 100-200 ng/ml
*P=0.01 vs. C2 700-1000 ng/ml
# CNI dose reduction and conversion

## Summary of RCT in Liver Tx

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Study population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlitt H et al</td>
<td>&gt;6 mo post-Tx</td>
<td>D/C CNI + initiation of MMF vs. continuation on CNI</td>
<td>6 mo follow-up&lt;br&gt;Scr ↓ 44.4 48.7 µmol/L in the study group vs. 3.1 14.3 in controls&lt;br&gt;Acute rejection: 3/14 study pts&lt;br&gt;Side effects: 8/14 study pts</td>
</tr>
<tr>
<td>Stewart SF et al</td>
<td>OLT &gt;1-yr</td>
<td>D/C CNI + initiation of MMF vs. continuation on CNI</td>
<td>Acute rejection 3/5 pts (re-Tx)</td>
</tr>
<tr>
<td>Pageaux G et al</td>
<td>OLT pts with renal dysfunction</td>
<td>Study group: 27&lt;br&gt;Control group: 29&lt;br&gt;Study group&lt;br&gt;MMF + 50%&lt;br&gt;CNI reduction&lt;br&gt;Control group&lt;br&gt;No MMF&lt;br&gt;CNI reduction (max 25%)&lt;br&gt;CrCl at 1-yr&lt;br&gt;Study group: 42.6 10.9 to 51.7 13.8 mL/min&lt;br&gt;Control group: 42.8 12.8 to 44.8 19.7 mL/min (p=0.04)&lt;br&gt;Rejection: 0 in study pts, 1 in controls&lt;br&gt;Death: 1 in study pts, 0 in controls&lt;br&gt;GI side-effects: 5 in study pts, 2 in controls</td>
<td>eGFR at 1-yr&lt;br&gt;Study group: 38.8 9.6 to 47.0 11.8 mL/min&lt;br&gt;Control group: No changes</td>
</tr>
<tr>
<td>Cinncinnati VR et al</td>
<td>OLT pts</td>
<td>Study group&lt;br&gt;MMF + CNI reduction&lt;br&gt;Control group&lt;br&gt;MMF + CNI No dose reduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart Tx</td>
<td>Liver Tx</td>
<td></td>
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<tr>
<td>--------------------------------</td>
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<td></td>
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<tr>
<td><strong>Renal function</strong></td>
<td><strong>Overall improvement</strong></td>
<td><strong>Overall improvement</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>Up to 5%</td>
<td>Up to 21%</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>Up to 14%</td>
<td>Up to 29%</td>
<td></td>
</tr>
<tr>
<td>Side-effects</td>
<td>Up to 76%</td>
<td>Up to 67%</td>
<td></td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>Up to 75%</td>
<td>Up to 34%</td>
<td></td>
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</table>

Summary of CNI-sparing strategies including pilot studies
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Management of CKD
Non-immunosuppressive strategies

• Hypertension
• Microalbuminuria / Proteinuria
• Anemia
• Hyperparathyroidism
• Evaluate pre-emptive kidney Tx
Conclusions

• CKD in Non-Renal TX patients is multi-factorial
• Prevention
  – Optimize immunosuppression
  – Treatment of co-morbidities
• Caution when converting patients
  – Acute rejection, side-effects
• Larger RCT are needed
• Long-term results are required
Future directions

• Determine the lower CNI dose to prevent acute and chronic rejection and minimize nephrotoxicity

• Determine the ideal CNI-sparing strategy that results in a stabilization of renal function w/o increasing rejection and side-effects
There are in fact two things: Science and opinion; the former begets knowledge, the latter begets ignorance