Calcineurin Inhibitor Nephrotoxicity: Renal Sparing Protocol by Evidence of Renal Dysfunction

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Overview

• CNIs (Calcineurin Inhibitors) and Renal Dysfunction
• Alternative Immunosuppression Therapies Once Renal Dysfunction Develops
• Drawbacks to Alternative Therapies
• Evolving Renal Dysfunction Screening Strategies
• Conclusions
Risk Factors for Acute and Chronic Kidney Disease in OLT Recipients

- **Age**
- **Systemic Hypertension**
- **Diabetes mellitus**
- **Hepatitis C/B**
- **Secondary IgA Nephropathy**
- **Chronic Glomerular Ischemia**
- **Hepatorenal Syndrome**
- **Oxalosis**
- **Renal function**

**Pretransplant**

**Acute Kidney Injury**

**Perioperative**

**Acute Kidney Injury**

**Posttransplant**

**Acute Kidney Injury**

- **Immunosuppressants**
- **Other Nephrotoxic drugs**
- **Reoperation**
- **IV Contrast**
- **Infection**

- **Immunosuppressants**
- **Other Nephrotoxic drugs**
- **Surgical Procedure**
- **IV Contrast**
- **Infection**

**Chronic Kidney Disease**
### Acute Renal Disease and Mortality Post-Liver Transplantation (Dublin series, n=359)

<table>
<thead>
<tr>
<th></th>
<th>30-day survival</th>
<th>P-value</th>
<th>1-year survival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function*</td>
<td>95.7%</td>
<td>-</td>
<td>78.4%</td>
<td>-</td>
</tr>
<tr>
<td>Acute Renal Injury</td>
<td>91.2%</td>
<td>0.25</td>
<td>76.5%</td>
<td>0.45</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>76.3%</td>
<td>&lt;0.001</td>
<td>47.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Acute renal injury ≥2-fold increase in preop SCr  
Acute renal failure ≥3-fold increase from preop SCr or renal replacement therapy  
*Reference group. P-value is in comparison to the reference group

O’Riodan A. Am J Transplant 2007;7:168-176
CNIs and Chronic Renal Dysfunction

- Recent 2002 Analysis 36,849 LT recipients
  - 1990 – 2000
  - 18.1% incidence CRI after 5 years
  - CNI dose and duration of exposure related

Renal Function Trend Post OLT

CNI and Renal Dysfunction

- CNIs cause renal dysfunction
- Renal dysfunction leads to increased mortality
- We agree that having a “renal sparing” approach is appropriate in patients that develop renal dysfunction
  - only 10-18% of all patients on CNI-based therapy
  - renal dysfunction is reversible with therapy conversion
Changing Therapy After Development of Renal Dysfunction: MMF and Sirolimus

- 134 LT recipients 12/94 – 12/02
  - Cyclosporin (CsA) 50 pts, Tacrolimus (TAC) 84 pts
- 10.4% of patients developed renal dysfunction
  - 7 pts dose reduction
    - Improved Cr @ 2 mo from 2.13 → 1.4 mg/dL (P=0.013)
  - 5 pts conversion mycophenolate mofetil (MMF), 2 pts to sirolimus
    - Cr @ 1 mo from 2.04 → 1.7 mg/dL (P=0.0026)
- No acute rejection after dose reduction or conversion
- Conclusions
  - ARF in early period increased risk of developing CRI
  - Clear improvement in renal function after dose reduction/conversion

Changing Therapy After Development of Renal Dysfunction: MMF

- 14 patients with renal dysfunction
  - switched from CNI to mycophenolate mofetil (MMF)
- Renal function improved in all patients after switch
- However, MMF monotherapy increased risk of rejection of 21.4% that resolved once CNIs were restarted.

Changing Therapy After Development of Renal Dysfunction: MMF

• 56 patients with CNI-induced CRI
  – 24 converted to MMF monotherapy
  – 37 converted to MMF and low dose CNI

• Results
  – Cal CrCl improved 100%
  – 19% acute rejection
    • Most severe in the MMF monotherapy arm

Bilboa, et al. IntImmunopharmacol 2006
Changing Therapy After Development of Renal Dysfunction: Sirolimus

- 31 pts switched from CNIs to SRLm
  - Mean Cr 1.9 → 1.2 mg/dL
  - Mean GFR 44.8 → 64.9 mL/min
- 4 pts (12.9%) developed acute cellular rejection biopsy proven

Why Wait?

- Starting a “renal sparing” approach before the *hypothetical* onset of renal dysfunction (10-18% of all patients) has no validity and may be harmful to the patient.
  - Increased acute rejection
  - Possible increased mortality in stable renal function patients
Conversion of CNI-based to Sirolimus in stable renal function

• Randomized Open Label Trial*
  – Submitted to FDA 3/25/09 by manufacturer of Sirolimus

• Sirolimus group compared to CNI continuation group
  – Fasting lipids significantly higher with Sirolimus
  – Suggested increased mortality with Sirolimus
  – Acute rejection significantly higher with Sirolimus

* A Randomized, Open-Label, Comparative Evaluation Of Conversion From Calcineurin Inhibitor Treatment to Sirolimus Treatment Versus Continuation Of Calcineurin Inhibitor Treatment In Liver Allograft Recipients Undergoing Maintenance Therapy
Black Box Warning for Sirolimus

• Information for Healthcare Professionals: Sirolimus (marketed as Rapamune)

FDA ALERT [06/11/2009]:
The FDA is notifying healthcare professionals of clinical trial data that suggest increased mortality in stable liver transplant patients after conversion from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus (Rapamune). The trial was conducted by sirolimus manufacturer, Wyeth.

• Sirolimus is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving kidney transplants. The safety and efficacy of this drug in liver or lung transplant patients have not been established by the FDA.

• The FDA is determining whether a labeling change for sirolimus is needed. In the interim, physicians should continue to use the drug’s professional labeling as a guide to therapy.

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Evolving Renal Dysfunction Strategies

• Urinary a1-microglobulin (a1mg) and b2-microglobulin (b2mg) in patient on CNIs
  – GFR measured directly by clearance 99mTc-DTPA
    • 1) GFR 97.4 mL/min, ↓7.3% from baseline
    • 2) GFR 85.6 mL/min, ↓16.7% from baseline
    • 3) GFR 62.3 mL/min, ↓32.5% from baseline
    • 4) GFR 49.6 mL/min, ↓52.4% from baseline
  – Cr only increased in group 4 with the most severe renal dysfunction
  – a1mg and b2mg increased in all 4 groups
• Available, inexpensive, and early marker for renal dysfunction
• Detect renal dysfunction earlier than Cr
  – Allowing for change in therapy before more severe renal damage

Conclusions

• Many factors can lead to CRI post OLT, of which CNIs can contribute
• Only 10-18% of pts on CNI-based therapy will develop CRI
  – reversible with therapy conversion
  – When renal failure occurs, a renal sparing immunosuppression protocol is indicated and well supported by the literature
• Alternative immunosuppressive therapies have many drawbacks
  – increased acute rejection, increased mortality in stable renal function patients
• New techniques to screen for early renal dysfunction
  – Allowing for change in therapy before more severe renal damage occurs
• 82-90% of patients on CNI-based protocols will not develop CNI-induced renal dysfunction, and those that do are reversible especially in early renal disease.
References