RENAL SPARING EFFECTS OF SIROLIMUS IN HIV+ TRANSPLANT RECIPIENTS

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Sirolimus may spare the nephrotoxic effects of calcineurin inhibitors (CNI), but has not been evaluated in the context of HIV.

Sirolimus may increase the risk of hypertriglyceridemia (hTG), especially with protease inhibitors (PI).

Significant drug interactions exist with the CNIs and sirolimus when used in combination with a PI or efavirenz (EFV) based antiretroviral (ARV) regimen.
Objectives

- Describe prevalence and indications for use of sirolimus in HIV+ kidney and liver transplant recipients
- Estimate impact of sirolimus on the estimated glomerular filtration rate (eGFR)
- Estimate impact of sirolimus on triglycerides (TG)
  - Describe use of lipid lowering therapy
- Describe sirolimus dosing modifications with ARVs
Methods

- Prospective, observational, multi-site study of liver or kidney transplantation in 112 HIV-infected patients
  - Retrospective collection of indications for sirolimus use in 26 (23%) patients
- Immunosuppression, ARV, and lipid lowering therapy individualized
- Univariate and multivariate repeated measures models to identify predictors of eGFR (4 point MDRD) and TG
eGFR Model Covariates

- Immunosuppression
  - Sirolimus vs CNI vs Sirolimus + CNI
- Protease inhibitor
- Tenofovir
- Co-trimoxazole
- Transplanted organ
- Gender, Race, Age
- Hepatitis C (HCV) status
- Donor source and age
- Rejection in the previous 3 months
- Time post transplant
- Baseline eGFR

Indications for sirolimus use not yet evaluated in this model
# Baseline Characteristics (N=26)

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus use Kidney (n=15)</th>
<th>Sirolimus use Liver (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>80</td>
<td>64</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>Other</td>
<td>87</td>
<td>45</td>
</tr>
<tr>
<td>HCV (%)</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>Donor source (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>Live</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Donor age (mean, years)</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Mean time (± SE) from txp to initiation of sirolimus (days)</td>
<td>162 ± 208</td>
<td>130 ± 140</td>
</tr>
<tr>
<td>Mean duration (± SE) of F/U (days)</td>
<td>323 ± 303</td>
<td>268 ± 247</td>
</tr>
</tbody>
</table>

* - duration of follow-up from time of conversion to sirolimus
# Indications for Sirolimus

<table>
<thead>
<tr>
<th>Indication</th>
<th>% patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction due to CNI’s</td>
<td>27% (7)</td>
</tr>
<tr>
<td>Tacrolimus (6), Cyclosporine (1)</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity secondary to CNI’s</td>
<td>22% (5)</td>
</tr>
<tr>
<td>Tacrolimus (3), Cyclosporine (2)</td>
<td></td>
</tr>
<tr>
<td>Preservation of renal function</td>
<td>15% (4)</td>
</tr>
<tr>
<td>Intolerance of anti-metabolite</td>
<td>12% (3)</td>
</tr>
<tr>
<td>Cyclosporine/Sirolimus site standard</td>
<td>8% (2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8% (2)</td>
</tr>
<tr>
<td>Rejection</td>
<td>8% (2)</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>4% (1)</td>
</tr>
</tbody>
</table>
## Results: Predictors of eGFR

### Kidney

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>-0.00417</td>
<td>0.0003</td>
</tr>
<tr>
<td>Rejection</td>
<td>-0.1426</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>0.2428</td>
<td>0.0002</td>
</tr>
<tr>
<td>Time post-transplant</td>
<td>-0.02154</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sirolimus + CNI</td>
<td>0.1365</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

### Liver

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>-0.00630</td>
<td>0.0207</td>
</tr>
<tr>
<td>Rejection</td>
<td>-0.06217</td>
<td>0.0412</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>0.1469</td>
<td>0.0158</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.1708</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

Final multivariate models
Estimates of eGFR in Kidney Recipients

- At year 1 post-transplant, assuming a median baseline eGFR (55) and donor age (38) the mean eGFR is estimated to be:
  - CNI: 57 ml/min/1.73m²
  - Sirolimus: 63 ml/min/1.73m²
  - Sirolimus and CNI: 78 ml/min/1.73m²

- The presence of a rejection episode in the past three months results in an additional 28% reduction in eGFR
Lipid Lowering Therapy

- Lipid lowering therapy was used in
  - 62% of subjects on sirolimus/PI therapy
  - 31% of subjects on sirolimus without a PI
  - 52% (45/86) of subjects who are not on sirolimus

- Sirolimus use was not associated with triglycerides in the multivariate model
Sirolimus Dosing

- Protease inhibitor based ARV regimen
  - Un-boosted PI regimen: 2 mg weekly
  - Boosted PI regimen: 0.5-2 mg weekly or 0.05 mg daily

- NNRTI based ARV regimen
  - Efavirenz: 3-6 mg daily
  - Nevirapine: 1-3 mg daily
Conclusions

- In this preliminary analysis, use of a CNI free sirolimus based IS regimen in HIV+ transplant recipients was not associated with higher eGFR
  - indications for sirolimus use, which may explain this finding, will be included in future modeling

- Triglyceride levels were also not associated with sirolimus

- Significant alterations in sirolimus dosing is necessary when used in combination with PI or efavirenz containing ARV regimens
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- New York, NY
  - Mt. Sinai School of Medicine (K, L, Peds K)
  - Columbia University (L, Peds L)
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    - University of Pittsburgh (K, L)
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