Optimal Use of mTOR Inhibitors

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I have financial relationship(s) within the last 12 months relevant to my presentation with:

Novartis: Grant/ Research, Consultant, Speakers Bureau

My presentation does include discussion of off-label or investigational use of Sirolimus and Everolimus

I do intend to reference unlabeled/unapproved uses of drugs or products in my presentation:

Use of everolimus and sirolimus (the entire presentation)
Proposed reasons to use mTOR inhibitors

• For GFR preservation
• For antineoplastic effects
• For cyst-reduction effects
• As a replacement agent for other agents due to side effects
  – For mycophenolate
  – For CNI
Proposed reasons NOT to use mTOR inhibitors

- Proteinuria
- Synergistic nephrotoxicity with CNI
- Wound healing
- Post-surgical events: lymphohocoele, delayed graft function
Proposed reasons to use mTOR inhibitors

• For GFR preservation
• For antineoplastic effects
• For cyst-reduction effects
• As a replacement agent for other agents due to side effects
  – For mycophenolate
  – For CNI
Why consider mTORi (or any other agent) for GFR? No improvements in graft survival despite newer agents, lower rejection rates

<table>
<thead>
<tr>
<th>Year</th>
<th>5 Year Adjusted Graft Survival, Kidney Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Living</td>
</tr>
<tr>
<td>1998-03</td>
<td>80.2%</td>
</tr>
<tr>
<td>1999-04</td>
<td>80.2%</td>
</tr>
<tr>
<td>2000-05</td>
<td>80.3%</td>
</tr>
<tr>
<td>2001-06</td>
<td>80.8%</td>
</tr>
<tr>
<td>2002-07</td>
<td>81.4%</td>
</tr>
</tbody>
</table>
CNI use in solid organ transplant, and the burden of chronic kidney disease

- **Organ** | **At Discharge** | **At 1 year**¹
- Liver | 97% | 93%
- Heart | 98% | 93%
- Lung | 100% | 92%


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**CKD (% with GFR<30)**²

² Ojo AO et al, NEJM 2003;349: 931
Biopsy-Diagnosed Renal Disease in Patients After Transplantation of Other Organs and Tissues

Non-renal transplant recipients with native renal biopsies:

<table>
<thead>
<tr>
<th>Biopsies</th>
<th>Liver n = 41</th>
<th>Lung n = 30</th>
<th>Heart n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after tx (mos)</td>
<td>35</td>
<td>19</td>
<td>66</td>
</tr>
<tr>
<td>eGFR at biopsy (mL/min)</td>
<td>37.6</td>
<td>28.1</td>
<td>25.1</td>
</tr>
<tr>
<td>Acute tubular injury</td>
<td>49%</td>
<td>75%</td>
<td>70%</td>
</tr>
<tr>
<td>IF/TA &gt;20%</td>
<td>51%</td>
<td>64%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Arteriolar hyalinosis</strong></td>
<td>13%</td>
<td><strong>64%</strong></td>
<td><strong>70%</strong></td>
</tr>
<tr>
<td>Benign nephrosclerosis</td>
<td>41%</td>
<td>54%</td>
<td>40%</td>
</tr>
<tr>
<td>Global glom. sclerosis</td>
<td>18%</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>13%</td>
<td>0</td>
<td>5%</td>
</tr>
<tr>
<td>Primary glom. disease</td>
<td>26%</td>
<td>0</td>
<td>15%</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>13%</td>
<td>14%</td>
<td>0</td>
</tr>
<tr>
<td>Polyoma virus nephropathy</td>
<td>0</td>
<td>4%</td>
<td>0</td>
</tr>
</tbody>
</table>

Schwarz A et al, AJT 2010;10: 2017
mTORi-based immunosuppression: When is it the “right” time?

Early

Late

De Novo? Within 1-6 months? At time of renal dysfunction?

Tx
The Symphony Trial: Defining today’s “Gold Standard”

- 12-month randomized open-label multicenter trial of 1645 KTX
- 4 Treatment arms: all receive Basiliximab induction, MMF/Prednisone
  - CSA 150-300 ng/ml x 3 months, then 100-200 ng/ml
  - CSA 50-100 ng/ml
  - TAC 3-7 ng/ml
  - SRL 4-8 ng/ml

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Acute Rejection (%)</th>
<th>Graft Survival (%)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>25.8</td>
<td>89.3</td>
<td>57.1</td>
</tr>
<tr>
<td>CSA “low”</td>
<td>24.0</td>
<td>93.1</td>
<td>59.4</td>
</tr>
<tr>
<td>TAC “low”</td>
<td>12.3*</td>
<td>94.2*</td>
<td>65.4*</td>
</tr>
<tr>
<td>SRL “low”</td>
<td>37.2</td>
<td>89.3</td>
<td>56.7</td>
</tr>
</tbody>
</table>
CNI avoidance with Sirolimus: true benefit?

Rabbit anti-thymocyte globulin x 5/MMF/Pred+
  SRL (15-20ng/ml x 4 mo, then 10-15 ng/ml)
vs. TAC (10-12ng/ml x 1 mo, 8-10ng/ml x 3 mo then 6-8 ng/ml)

• At 1 year:  
  SRL group (n=81)  
  TAC group (n=84)

  Acute rejection  13.0%  10.0% (p=ns)
  GFR @1y  56 ml/min  55 ml/min (p=ns)
  GFR @2y  55 ml/min  55 ml/min (p=ns)

• Biopsy data @1y:  
  chronic vascular changes:  26%  43% (p=0.03) (cv1 or greater)
  *no differences in interstitial fibrosis, tubular atrophy, or glomerulopathy

• Discontinuation rate  38%  16%

Larson TS et al, Am J Transplantation 2006;6: 514
mTORi-based immunosuppression: When is it the “right” time?

Early

- De Novo?
- Within 1-6 months?

Late

- At time of renal dysfunction?
The CONVERT study: Can CNIs be withdrawn later after transplant to preserve renal function?

CNI* (n=830)
6 months to 120 months posttransplant

Randomization
Mean of 3.2 years after kidney transplantation

CNI*
(n=275)
Baseline GFR
STRATUM 1: 20-40 mL/min: n=29
STRATUM 2: >40 mL/min: n=246

Sirolimus*
(n=555)
Baseline GFR
STRATUM 1: 20-40 mL/min: n=58
STRATUM 2: >40 mL/min: n=497

* Concomitant medications included mycophenolate mofetil (MMF) or azathioprine (AZA), and corticosteroids
* 93% of patients in the SRL arm and 88% of patients in the CNI arm had CAN≥1

Late conversion from CNI to SRL: no benefit, potential for harm

(ITT Analysis, baseline GFR > 40 mL/min)

<table>
<thead>
<tr>
<th></th>
<th>SRL conversion</th>
<th>CNI continuation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 month eGFR (mL/min)</td>
<td>59.0</td>
<td>57.7</td>
<td>0.28</td>
</tr>
<tr>
<td>24 month eGFR (mL/min)</td>
<td>53.7</td>
<td>52.1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

• Late conversion to a sirolimus-based regimen showed no renal function benefit, with worsening proteinuria:
  – Release of CsA-induced afferent arteriolar vasoconstriction\(^1\), antagonism of VEGF\(^2\), loss of nephrin expression with mTOR\(^3\) are potential mechanisms


CNI Withdrawal in the setting of graft dysfunction: are there subgroups that benefit?

- 159 patients underwent transition from TAC/MMF/P to SRL/MMF/P
- Baseline biopsy: IF/TA score 1.01 (NOT SEVERE “CAN!”)
  - Baseline proteinuria: UACR 98 (NOT SEVERE GLOMERULAR INJURY!)
- Of 136 who remained on SRL >90d, 101 (76%) improved eGFR:
  - Time to conversion = 17 months in responders vs 34 months in nonresponders
  - Baseline eGFR = 28 ml/min in responders vs 19 ml/min in nonresponders, p=0.001
CNI withdrawal with SRL vs. CNI reduction in heart tx recipients with CKD

63 HTx pts with GFR<60
CNI/MMF/±Pred (CsA>100 or TAC>9)

Randomization: mean 5.8y from transplant

- **SRL (8-14 ng/ml)**
- CNI tapered, discontinued when SRL therapeutic (mean 2.6 weeks) (n=30*)

- **CNI reduction by 40% over 4 weeks** (n=33)

Groetzner J et al, *Transplantation* 2009; 87: 726
CNI withdrawal with SRL vs. CNI reduction in heart tx recipients with CKD

- Renal function significantly better with CNI withdrawal:
  - n=0 initiated dialysis in CNI withdrawal
  - n=6 initiated dialysis in CNI reduction arm

- No difference in rejection
  - 4 in CNI reduction
  - 2 in SRL

- Higher rate of side effects in CNI withdrawal (SRL) primarily dermatologic

In those not initiating dialysis:

>10 ml/min improvement in GFR with SRL transition/CNI discontinuation

Groetzner J et al, Transplantation 2009; 87: 726
mTORi-based immunosuppression: When is it the “right” time?

Early

De Novo?

Late

Within 1-6 months?

At time of renal dysfunction?

Tx
“MMF-based immunosuppression with SRL: The Spare-the-Nephron trial”

Open label, prospective, randomized, multi-center study

Patients Post-Transplant Maintained on CNI+MMF ± Steroids

30-180 Days Randomization n=305

CNI+MMF
MMF 1-1.5 g BID

Sirolimus+ MMF
MMF 1-1.5 g BID
SRL Loading Dose: 2-10 mg
SRL trough: 5-10 ng/mL

<table>
<thead>
<tr>
<th></th>
<th>MMF/SRL n=148</th>
<th>MMF/CNI n=151</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Change in eGFR at 24 months</td>
<td>+9.8%</td>
<td>+2.1%</td>
</tr>
<tr>
<td>BPAR, %</td>
<td>9.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Graft Loss, %</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Death, %</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>Proportion of Patients DC Treatment for AEs,%</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

Weir MR et al, Kidney Int. 2010 Dec 29
Conversion to EVR/ MMF/Steroids vs CsA/MMF/Steroids at 4.5 months post-renal transplant

The ZEUS Study

Multi-center, randomized, controlled trial in 300 renal transplant recipients

IL2ra + CsA/MPA/Steroids n=503

300 Randomized at Month 4.5

Group A: **Everolimus**: 6-10 ng/mL to M12 + MPA 1440 mg/d + steroids

Group B: CsA 125-175 ng/mL to M6, 100-150 ng/mL to M12 + MPA 1440mg/d + steroids

300 Randomized at Month 4.5

At 12 months:

<table>
<thead>
<tr>
<th></th>
<th>EVR/MPA/Steroids n=154</th>
<th>CsA/MPA/Steroids n=146</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, Nankivell</td>
<td>71.8 ml/min</td>
<td>61.9 ml/min</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient Survival</td>
<td>99%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>Death Censored Graft Survival</td>
<td>100%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>BCAR after randomization</td>
<td>10%</td>
<td>3%</td>
<td>0.04</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>24%</td>
<td>19%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Higher rates of proteinuria, stomatitis, hyperlipidemia treatment in mTORi arm

A Randomized, Multi-Center Trial of Early Conversion to SRL/MMF/Steroids vs CsA/MMF/Steroids in Renal Transplantation

**The SMART Study**

Multi-center, randomized, controlled trial in 196 renal transplant recipients

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**Group A:** Sirolimus: 8-12 ng/mL to M3, then 5-10 ng/mL to M12 + MMF 1.5 g/d + steroids

**Group B:** CsA 150-200 ng/mL to M3, then 100-150 ng/mL to M12 + MMF 2 g/d + steroids

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### Creatinine Clearance, Nankivell

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine Clearance, Nankivell</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>65.2 ml/min</td>
<td>0.004</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>54.1 ml/min</td>
<td></td>
</tr>
</tbody>
</table>

### Creatinine Clearance, MDRD

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine Clearance, MDRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>55.3 ml/min</td>
<td>0.03</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>47.3 ml/min</td>
<td></td>
</tr>
</tbody>
</table>

### Patient Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>98.6</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>98.6</td>
</tr>
</tbody>
</table>

### Death Censored Graft Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Death Censored Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>100</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>98.6</td>
</tr>
</tbody>
</table>

### BCAR

<table>
<thead>
<tr>
<th>Group</th>
<th>BCAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>23.2</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>19.7</td>
</tr>
</tbody>
</table>

### Discontinuations

<table>
<thead>
<tr>
<th>Group</th>
<th>Discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>36.2</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>19.7</td>
</tr>
</tbody>
</table>

### CMV Viremia

<table>
<thead>
<tr>
<th>Group</th>
<th>CMV Viremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/MMF/Steroids</td>
<td>5.8</td>
</tr>
<tr>
<td>CsA/MMF/Steroids</td>
<td>26.8</td>
</tr>
</tbody>
</table>

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“Early Withdrawal of Calcineurin Inhibitors and Everolimus Monotherapy in de novo Liver Transplant Recipients Preserves Renal Function”

Il2ra/CsA/Steroids
Pred taper off by 5 weeks posttransplant

Day 10 Randomization

Everolimus (8-10 ng/ml)
CsA discontinued at 4 weeks (n=52)

CsA Maintenance
CsA target 225-200-150 over 12mo (If CNI complications, +MMF with CsA target 100 ng/ml) (n=26)

Masetti M et al, AJT 2010; 10: 2252
Early Withdrawal of CsA with Everolimus Monotherapy results in better GFR at 1y in de novo OLTx

\[
\begin{align*}
eGFR \text{ at 1y:} \\
\text{CsA} & \quad 59.9 \text{ ml/min} \\
\text{EVR} & \quad 87.7 \text{ ml/min}
\end{align*}
\]

\[
\begin{align*}
\% \text{ CKD} \geq 3 \text{ at 1y:} \\
\text{CsA} & \quad 52.2\% \\
\text{EVR} & \quad 14.4\%
\end{align*}
\]

Masetti M et al, AJT 2010; 10: 2252
mTORi-based immunosuppression for GFR: Conclusions

<table>
<thead>
<tr>
<th>Graft Outcomes (GFR, rejection, biopsy data)</th>
<th>De novo</th>
<th>1-6 mo</th>
<th>&gt; 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>Yes and no</td>
<td>No and yes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Commentary</th>
<th>De novo</th>
<th>1-6 mo</th>
<th>&gt; 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection higher, surgical complications a concern, large trials do not support</td>
<td>Multiple studies consistently show improved GFR despite increased risk of acute rejection</td>
<td>Depends on biopsy findings/proteinuria: not advisable in patients with proteinuria</td>
<td></td>
</tr>
</tbody>
</table>

Early Late

Have we been successful?
Proposed reasons to use mTOR inhibitors

- For GFR preservation
- For antineoplastic effects
- For cyst-reduction effects
- As a replacement agent for other agents due to side effects
  - For mycophenolate
  - For CNI
mTOR inhibition and malignancy

- 1996-2001 registry data (f/u censored at 963d)
- mTOR use associated with significantly lower rates of malignancy

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>Number of transplants</th>
<th>De novo malignancy</th>
<th>De novo nonskin solid malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL/ERL</td>
<td>504</td>
<td>0.60</td>
<td>0.0</td>
</tr>
<tr>
<td>SRL/ERL + CNI</td>
<td>2321</td>
<td>0.60</td>
<td>0.47</td>
</tr>
<tr>
<td>CNI</td>
<td>30,424</td>
<td>1.81*</td>
<td>1.00*</td>
</tr>
</tbody>
</table>

- Rapamune Maintenance Regimen (RMR) trial, SRL/ST vs SRL/CSA/ST
- on-therapy analysis of malignancy:
- mTOR use associated with significantly lower rates of malignancy

Campistol JM et al. J ASN 2006;17:581
Sirolimus for Kaposi's Sarcoma in Renal-Transplant Recipients

• In 15 renal-transplant recipients with cutaneous Kaposi's sarcoma, cyclosporine was stopped and sirolimus was started
• All skin lesions in all patients regressed within six months, likely due to inhibition of VEGF and AKT signalling in tumor cells
• No episodes of rejection or deterioration in GFR at 6 months

mTOR inhibition provided benefit in survival and prevention of disease progression in late-stage renal cell carcinoma.

626 patients with newly diagnosed metastatic renal-cell cancer:

<table>
<thead>
<tr>
<th>End point</th>
<th>IFN</th>
<th>Temsirolimus</th>
<th>IFN + Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>7.3 mo</td>
<td>10.9 mo</td>
<td>8.4 mo</td>
</tr>
<tr>
<td>“Clinical benefit”</td>
<td>15.5%</td>
<td>32.1%</td>
<td>28.1%</td>
</tr>
</tbody>
</table>

Hudes G et al. NEJM 2007;356:2271
Switch to SRL for skin cancer in long-term renal transplant recipients:

Randomized, prospective, assessor-blinded study

44 KTX patients with premalignant/malignant skin changes

25 pts SRL transition

19 pts usual care

<table>
<thead>
<tr>
<th>Clinical assessment (month 12)</th>
<th>Arm A (sirolimus) n (Patients)</th>
<th>%</th>
<th>Arm B (control) n (Patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = Marked worsening</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>2 = Worsening</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>11.8</td>
</tr>
<tr>
<td>3 = Slight worsening</td>
<td>0</td>
<td>0.0</td>
<td>10</td>
<td>58.8</td>
</tr>
<tr>
<td>4 = Unchanged</td>
<td>4</td>
<td>26.7</td>
<td>5</td>
<td>29.4</td>
</tr>
<tr>
<td>5 = Slight improvement</td>
<td>6</td>
<td>40.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>6 = Improvement</td>
<td>4</td>
<td>26.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>7 = Marked improvement</td>
<td>1</td>
<td>6.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>100.0</td>
<td>17</td>
<td>100.0</td>
</tr>
</tbody>
</table>

New skin ca: 1

Salgo R et al. AJT 2010; 1385
Conclusions-mTORi and Malignancy

- mTORi appears to have both immunosuppressive and antineoplastic effects, and may provide a practical advantage in graft recipients with Kaposi's sarcoma, skin cancer and other neoplasms that arise in immunosuppressed patients
Proposed reasons to use mTOR inhibitors

• For GFR preservation
• For antineoplastic effects
• For cyst-reduction effects
• As a replacement agent for other agents due to side effects
  – For mycophenolate
  – For CNI
Rationale

• In autosomal dominant polycystic kidney disease (ADPKD), aberrant activation of mTOR pathway is associated with progressive kidney enlargement

• 2 multicenter randomized controlled trials in early CKD for impact of mTOR inhibition on cyst/kidney volume

Serra AL et al. NEJM 2010;363:820
Walz G et al. NEJM 2010;363:830
Sirolimus and Kidney Growth in ADPKD

Sirolimus vs placebo in an 18-month open-label, randomized, controlled trial of 100 adults with ADPKD and early CKD (eGFR 92 ml/min, 43% on RAS agents)

- Sirolimus 2 mg/d did not halt polycystic kidney growth
- (<7% had CKD III as baseline, so no impact on GFR was expected)

Serra AL et al. NEJM 2010;363:820
Everolimus in Patients with ADPKD

2-year, double-blind trial of 433 patients with ADPKD randomly assigned to receive either placebo or everolimus to determine effect on kidney/cyst size (via MRI), baseline GFR 55 ml/min, 80% on RAS agents

• Everolimus slowed the increase in kidney volume by MRI, but did not slow the progression of renal impairment

Walz G et al. NEJM 2010;363:830
Proposed reasons to use mTOR inhibitors

• For GFR preservation
• For antineoplastic effects
• For cyst-reduction effects
• As a replacement agent for other agents due to side effects
  – For mycophenolate
  – For CNI
Large database analysis supported TAC/MMF vs. TAC/SRL from 2000-2004

<table>
<thead>
<tr>
<th>Regimen</th>
<th>One Year Graft Survival</th>
<th>Three Year Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC/MMF</td>
<td>94.2</td>
<td>85.9</td>
</tr>
<tr>
<td>CsA/MMF</td>
<td>92.9</td>
<td>85.3</td>
</tr>
<tr>
<td>CsA/SRL</td>
<td>92.8</td>
<td>82.2</td>
</tr>
<tr>
<td>TAC/SRL</td>
<td>91.8</td>
<td>80.3</td>
</tr>
</tbody>
</table>

**Tac/SRL vs. Tac/MPA as Maintenance Immunosuppression in Adult Renal Transplantation**

354 patients from 2003-2006 at a single center

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Mean Tac trough at 1 Yr</th>
<th>AR at 1 Yr (%)</th>
<th>Mean 1Yr GFR (ml/min)</th>
<th>3 Yr Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC/SRL (191)</td>
<td>6.6</td>
<td>7.9</td>
<td>57.9#</td>
<td>88.2%</td>
</tr>
<tr>
<td>TAC/MPA (163)</td>
<td>6.9</td>
<td>12.9</td>
<td>63.0</td>
<td>88.9%</td>
</tr>
</tbody>
</table>

#p=0.01

TAC/SRL well tolerated, but highlighted greater emphasis on reduced CNI trough goals

Gralla J and Wiseman AC, Transplantation 2009; 87: 1712
mTORi in place of MPA, with CsA Minimization

- Everolimus and Very Low CSA Exposure in De Novo Renal Transplant

**Mean Trough CSA Level, ng/mL**

- **EVR + reduced-dose CsA (n = 274)**
- **MPA + standard-dose CsA (n = 274)**

**GFR at Month 12**

<table>
<thead>
<tr>
<th></th>
<th>EVR 3-8 ng/mL</th>
<th>MPA 1.44 g</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR at Month 12</strong></td>
<td>54.6</td>
<td>52.2</td>
</tr>
<tr>
<td><strong>Treated BPAR</strong></td>
<td>16.2%</td>
<td>17.0%</td>
</tr>
<tr>
<td><strong>Graft loss</strong></td>
<td>4.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>Any wound event</strong></td>
<td>35.0%</td>
<td>25.6%</td>
</tr>
<tr>
<td><strong>Total infections</strong></td>
<td>61.7%</td>
<td>67.8%</td>
</tr>
<tr>
<td><strong>CMV</strong></td>
<td>1.1</td>
<td>8.4</td>
</tr>
<tr>
<td><strong>BKV</strong></td>
<td>0.7</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**Data Source:** Tedesco-Silva et al, Am J Transplant 2010; 10: 1401
Optimal use of mTOR inhibitors

• For GFR preservation: mixed bag; stable lower-risk patients can be converted to mTOR from CNI. Liver/heart tx data similar to renal data

• For antineoplastic effects: provocative; consistent trends in most studies support mTORi use

• For cyst-reduction effects: experimental data have not translated into clinical success

• Can be considered as a replacement agent for mycophenolate, both at time of transplant and as substitute for side effects, *but CNI exposure should be minimized*

• Avoid: patients with proteinuria or significant fibrosis, uncontrolled hyperlipidemia, obesity/risk of wound healing