IMMUNOSUPPRESSION: where do we stand in 2016?

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• Mycophenolic acid
• Tacrolimus
• Ciclosporine A vs. Tacrolimus
• mTOR-inhibitors
• Belatacept
MYCOPHENOLIC ACID
Fixed- or controlled-dose MMF with CNIs?

• **Opticept trial** (Gaston RS et al., AJT, 2009; 9: 1607-19.)
  
  – 2y study in 720 *de novo* KTx patients (MMF-concentration controlled (CC) + reduced CNI or MMF-CC + sdt CNI or fixed-dose MMF and sdt CNI
    
    • No differences in BPAR, patient and graft survival

• **FDCC trial** (van Gelder T et al, Transplantation, 2008; 86: 1043-51)
  
  – 1y study in 891 *de novo* KTx receiving either MMF fixed-dose or CC MMF in addition to CNI sdt dose
    
    • No difference in treatment failure
MPA and drug exposure: consensus meeting

• “Because of variability in the dose-concentration relationship, MPA exposure should be measured and doses should be adjusted accordingly to achieve optimal clinical outcomes.”

• “MPA exposure should be measured in the first week after transplant, then each week for the first month, each month until month 3, and subsequently every 3 months up to 1 year with appropriate dose adjustment, as AUC is likely to increase over time”.

• For MMF, bayesian models to predict AUC 0-12 have been implemented based on 3 to 4 time points results.

• “In patients taking EC-MPS AUC 0-12 measurement is still necessary to obtain reliable estimates of MPA exposure”.

Controlled-dose versus fixed-dose mycophenolate mofetil for kidney transplant recipients: a systematic review and meta-analysis of randomized controlled trials (1)

General study characteristics of eligible trials included in the systematic review

<table>
<thead>
<tr>
<th>Trials</th>
<th>No. KTRs</th>
<th>Induction/maintenance immunosuppression</th>
<th>Intervention</th>
<th>Main outcomes</th>
<th>Follow-up duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOMYGRE 2007</td>
<td>130</td>
<td>IL2-RA/CsA+MMF±Pred</td>
<td>CD: target MPA AUC of 40 mg hr/L; FD: MMF 2 g/d</td>
<td>Acute rejection, death, GI AEs, graft function, graft loss, hematologic AEs, infection, MMF discontinuation, treatment failure</td>
<td>12 mo</td>
</tr>
<tr>
<td>FDCC 2008</td>
<td>901</td>
<td>Multiformity/CNI+MMF+Pred</td>
<td>CD: target MPA AUC of 45 mg hr/L; FD: MMF 2 g/d for adults and 1.2 g/m²/d for pediatrics</td>
<td>Acute rejection, death, GI AEs, graft loss, hematologic AEs, infection, malignancy, MMF discontinuation, treatment failure</td>
<td>12 mo</td>
</tr>
<tr>
<td>OPTICEPT 2009</td>
<td>477</td>
<td>Multiformity/CNI+MMF+Pred</td>
<td>CD: target MPA trough level ≥1.3 mg/L (CsA) and ≥1.9 mg/L (FK); FD: MMF 2 g/d for adults and 1.2 g/m²/d for pediatrics</td>
<td>Acute rejection, death, GI AEs, graft loss, hematologic AEs, infection, malignancy, MMF discontinuation, treatment failure</td>
<td>2 yr</td>
</tr>
<tr>
<td>OPERA 2011</td>
<td>247</td>
<td>IL2-RA/CsA+MMF±Pred</td>
<td>CD: target MPA AUC of 40 mg hr/L; FD: MMF 2 g/d</td>
<td>Acute rejection, death, GI AEs, graft function, graft loss, hematologic AEs, infection, MMF discontinuation, treatment failure</td>
<td>12 mo</td>
</tr>
</tbody>
</table>

AEs, adverse events; AUC, area under the curve; CD, controlled-dose; CNI, calcineurin inhibitor; CsA, cyclosporine; FD, fixed-dose; FK, tacrolimus; GI, gastrointestinal; IL2-RA, interleukin-2 receptor antagonist; KTRs, kidney transplant recipients; MMF, mycophenolate mofetil; MPA, mycophenolic acid; Pred, prednisolone.
Controlled-dose versus fixed-dose mycophenolate mofetil for kidney transplant recipients: a systematic review and meta-analysis of randomized controlled trials (2)

Methodology of the pharmacokinetic measurement of MPA exposure

<table>
<thead>
<tr>
<th>Trials</th>
<th>Method of MPA quantification</th>
<th>Time points of samplings (after MMF administration)</th>
<th>MPA AUC calculation</th>
<th>Schedule for TDM (posttransplantation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOMYGRE 2007</td>
<td>HPLC</td>
<td>20 min and 1 and 3 hr</td>
<td>Bayesian estimation</td>
<td>Days 7 and 14, months 1, 3, 6, and 12</td>
</tr>
<tr>
<td>FDCC 2008</td>
<td>EMIT (53%), HPLC (47%)</td>
<td>0, 30, and 120 min</td>
<td>Multiple regression</td>
<td>Days 3 and 10, week 4, months 3, 6, and 12</td>
</tr>
<tr>
<td>OPTICEPT 2009</td>
<td>NR</td>
<td>0, 30, and 120 min</td>
<td>NR</td>
<td>Days 3, 10, and 30, months 3, 6, and 12</td>
</tr>
<tr>
<td>OPERA 2011</td>
<td>HPLC</td>
<td>20 min and 1 and 3 hr</td>
<td>Bayesian estimation</td>
<td>Weeks 2, 6, 12, 26, and 52</td>
</tr>
</tbody>
</table>

* MMF doses were adjusted based on trough levels, although abbreviated AUCs were also determined during the trial.

AUC, area under the curve; EMIT, enzyme multiplied immunoassay technique; HPLC, high-performance liquid chromatography; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NR, not reported; TDM, therapeutic drug monitoring.
Controlled-dose versus fixed-dose mycophenolate mofetil for kidney transplant recipients: a systematic review and meta-analysis of randomized controlled trials (3)

**A**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Controlled-Dose</th>
<th>Fixed-Dose</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOMYGRE 2007</td>
<td>19 Events, 65 Total</td>
<td>31 Events, 65 Total</td>
<td>12.0%</td>
<td>0.61 [0.39, 0.97]</td>
<td>2007</td>
</tr>
<tr>
<td>FDCC 2008</td>
<td>115 Events, 449 Total</td>
<td>116 Events, 452 Total</td>
<td>44.9%</td>
<td>1.00 [0.80, 1.25]</td>
<td>2008</td>
</tr>
<tr>
<td>OPTICEPT 2009</td>
<td>50 Events, 237 Total</td>
<td>57 Events, 240 Total</td>
<td>22.0%</td>
<td>0.89 [0.64, 1.24]</td>
<td>2009</td>
</tr>
<tr>
<td>OPERA 2011</td>
<td>62 Events, 126 Total</td>
<td>53 Events, 121 Total</td>
<td>21.0%</td>
<td>1.12 [0.86, 1.47]</td>
<td>2011</td>
</tr>
</tbody>
</table>

Total (95% CI) 877 Events, 878 Total 100.0% 0.95 [0.82, 1.10]

Total events 246 257

Heterogeneity: Chi² = 5.37, df = 3 (P = 0.15); I² = 44%

Test for overall effect: Z = 0.64 (P = 0.52)

Forest plot showing the risk ratio of posttransplantation treatment failure

Wang X et al. Transplantation 2013;93:361-367
Controlled-dose versus fixed-dose mycophenolate mofetil for kidney transplant recipients: a systematic review and meta-analysis of randomized controlled trials (4)

Forest plot showing the risk ratio of posttransplantation infection

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Controlled-Dose Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H. Fixed. 95% CI Year</th>
<th>Risk Ratio M-H. Fixed. 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOMYGRE 2007</td>
<td>50</td>
<td>65</td>
<td>48</td>
<td>17.6%</td>
<td>1.04 [0.86, 1.27] 2007</td>
</tr>
<tr>
<td>FDCC 2008</td>
<td>132</td>
<td>449</td>
<td>117</td>
<td>42.9%</td>
<td>1.14 [0.92, 1.40] 2008</td>
</tr>
<tr>
<td>OPTICEPT 2009</td>
<td>30</td>
<td>233</td>
<td>25</td>
<td>9.1%</td>
<td>1.23 [0.74, 2.02] 2009</td>
</tr>
<tr>
<td>OPERA 2011</td>
<td>103</td>
<td>127</td>
<td>82</td>
<td>30.4%</td>
<td>1.24 [1.06, 1.44] 2011</td>
</tr>
</tbody>
</table>

Total (95% CI) 874 880 100.0% 1.16 [1.03, 1.30]

Total events 315 272

Heterogeneity: Chi² = 1.91, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)
Controlled-dose versus fixed-dose mycophenolate mofetil for kidney transplant recipients: a systematic review and meta-analysis of randomized controlled trials (4)

### Meta-analysis results of CD versus FD MMF for each component of treatment failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCTs (n)</th>
<th>Incidence (CD vs. FD)</th>
<th>Relative risk (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection(^\text{a})</td>
<td>4</td>
<td>18.9% (166/877) vs. 18.6% (163/878)</td>
<td>0.97 (0.66–1.42)</td>
<td>0.04 65%</td>
</tr>
<tr>
<td>BPAR</td>
<td>4</td>
<td>14.4% (126/877) vs. 14.5% (127/878)</td>
<td>0.95 (0.59–1.52)</td>
<td>0.02 68%</td>
</tr>
<tr>
<td>SCAR</td>
<td>1</td>
<td>9.3% (8/86) vs. 10.0% (8/80)</td>
<td>0.93 (0.37–2.36)</td>
<td>—</td>
</tr>
<tr>
<td>Graft loss</td>
<td>4</td>
<td>3.4% (30/877) vs. 4.6% (40/878)</td>
<td>0.75 (0.47–1.19)</td>
<td>0.70 0</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>2.3% (20/877) vs. 2.8% (25/878)</td>
<td>0.80 (0.45–1.43)</td>
<td>0.44 0</td>
</tr>
<tr>
<td>MMF discontinuation</td>
<td>4</td>
<td>8.2% (72/877) vs. 8.8% (77/878)</td>
<td>0.93 (0.69–1.27)</td>
<td>0.95 0</td>
</tr>
</tbody>
</table>

\(^\text{a}\) Acute rejection includes BPAR, SCAR at protocol biopsy, and presumptive acute rejection without biopsy performed.

BPAR, biopsy-proven acute rejection; CD, controlled-dose; CI, confidence interval; FD, fixed-dose; MMF, mycophenolate mofetil; RCT, randomized controlled trials; SCAR, subclinical acute rejection.

**NO difference at all between CC and FD**

Wang X et al. Transplantation 2013;93:361-367
Efficacy and safety of intensified EC-MPS with low exposure of CNI in Chinese de novo KTx recipients (1)

- A 6-month single center study prospective study between 01-2014 and 02-2015

- Patients: 97 de novo Chinese KTx recipients on EC-MPS-based immunosuppression (+CNIs with steroids; induction with ATG or basiliximab)

- Two groups:
  - Intensified ECMPS: 1800-2160 mg/d for W1-2; 1440 mg/d W2-4; 720-1440 mg/d thereafter
  - Standard ECMPS: 1080-1440 mg/d W1-4, and 720-1440 mg/d thereafter.
  - Follow-up: 6 months

- Tacrolimus: 5-8 ng/mL; CsA: 150-200 ng/mL W1-4, then 120-180 M1-3, thereafter 100-150 ng/mL.

Kaplan–Meier analysis of freedom from acute rejection

Efficacy and safety of intensified EC-MPS with low exposure of CNI in Chinese de novo KTx recipients (3)

Comparison of renal allograft function in patients receiving either intensified EC-MPS dosing or standard dosing at day 0, 1, 3, 7, 14, 30, 90 and 180 post transplant. (A) Serum creatinine, linear mixed effect model, adjusted for gender and baseline data, p = 0.70. (B) eGFR, linear mixed effect model, adjusted for baseline data, p = 0.61. EC-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate. Produced by GraphPad Prism version 6.02 (GraphPad Software Inc., La Jolla, CA)

• MPA monitoring with aiming at an AUC > > 30 (or 40) µg•h/mL is associated with:
  – significantly less acute rejection episodes
  – Same patient and graft survival in the mid-term

  – *Hence, I think that there is NO need to monitor MPA based on AUC (or trough) levels*
Tacrolimus-based immunosuppression
The state-of-the-art immunosuppression in kidney transplantation has been based on CNIs for the last 3 decades.

- Tacrolimus is nowadays the preferable CNI, i.e. it is used more often than ciclosporin (CsA).
  - Because CNIs are nephrotoxic
    - Minimization strategies, e.g. **Symphony** trial
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Standard-dose CsA</th>
<th>Low-dose CsA</th>
<th>Low-dose Tac</th>
<th>Low-dose SRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>2 g CellCept®</td>
<td>2 g CellCept®</td>
<td>2 g CellCept®</td>
<td>2 g CellCept®</td>
</tr>
<tr>
<td>Daclizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symphony study: 1,645 patients**

- 150-300 ng/mL for 3 months
- 100-200 ng/mL thereafter
Biopsy Proven Acute Rejection at 1 year
*(ITT, Excluding Borderline)*

![Bar chart showing BPAR (% of patients) over 12 months post-Tx.](chart)

- Normal-dose CsA: 26%
- Low-dose CsA: 24%
- Low-dose TAC: 12%
- Low-dose SRL: 37%

p<0.0001 between Normal-dose CsA and Low-dose CsA,
p<0.0001 between Normal-dose CsA and Low-dose SRL,
p<0.0001 between Low-dose CsA and Low-dose SRL.

Ekberg *et al.*, NEJM 2007
Graft survival censored for patient death with a functioning graft in the four treatment groups. The analysis is based on the entire ITT population of the core study and patients not participating in the follow-up from 1 year onward are censored at their last visit.

Renal function over time (week 1–month 36, mean Cockcroft–Gault estimated GFR, without imputation and without carrying forward of serum creatinine values). The analysis is based on the entire ITT population of the core study, i.e. the first year also includes patients who did not participate in the follow-up.
Tacrolimus and pharmacokinetics
Tacrolimus bid (Prograf) vs. Prolonged release tacrolimus (Advagraf) (once a day)
1. Non-randomized, parallel-group study

- Slightly slower absorption profile with Advagraf®
- Slightly better correlation between $AUC_{0-24h}$ and $C_0$

○ TAC-BID (n = 47)
• TAC-OD (n = 25)

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Niioka et al., Transplantation. 2012;94:1013-9
Similar $\text{AUC}_{0-24\text{h}}$ but lower $C_0$ with Advagraf$^\text{®}$ → tendency to increase the dose

Niioka et al., Transplantation. 2012;94:1013-9
Our experience with Advagraf® PK

Advagraf® PK profiles
(45 renal transplant patients, stable post-transplant period)

AUC_{0-24}/dose: CV% = 47%
Randomized parallel group study in *de novo* KTx

34 patients on Tac OD and 32 on TAC BID

Wlodarczyk et al., Am J Transplant. 2009
Advagraf® vs. Prograf®: Summary

• *De novo* renal transplant patients
  – $\text{AUC}_{0-24h}$ lower by ~30% on Day 1
  – Comparable $C_0$ as soon as Day 4, provided the dose is increased
  – Variable PK profiles amongst patients

• Conversion 1:1 $\rightarrow$ $C_0$ decreased by 10-15%, while $\text{AUC}_{0-24h}$ is only decreased by ~ 5% on average
How to improve tacrolimus bioavailability by increasing its absorption?
Improving GI absorption of tacrolimus

- Tacrolimus is poorly soluble in water - causes low and variable absorption
- MeltDose® enhances the bioavailability of tacrolimus, by melting the particles
- The melted tacrolimus is sprayed by a controlled, heated system to produce a “controlled agglomeration” of amorphous tacrolimus
- Tablets are compressed for once-daily dosing
- MeltDose® applied to tacrolimus: LCP Tacro or Envarsus® (Prolonged release tablets)
**Envarsus®: Improved Formulation Enables Flatter PK Curve**

- Similar exposure with significantly lower peak ($P=.0001$)
- Significantly lower peak-to-trough fluctuation ($P=.0001$) at steady state
- Characteristic fluctuation and therapeutic range:
  - Envarsus® ~ 7-12 ng/ml
  - Prograf® ~ 6-16 ng/mL
- Peak concentration: 6 hours for Envarsus® vs. 2 hours for Prograf®

Gaber et al, Transplantation 2013; 96: 191–197
Envarsus® vs. Advagraf® in healthy volunteers

PK cross-over study over 10 days
Envarsus® (2 mg) vs. Advagraf® (2 mg)

**PK parameters for Tacrolimus on Day 10**

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>LCP-Tacro</th>
<th>Advagraf</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24}$ (ng·hr/mL)</td>
<td>142.27 ± 49.41</td>
<td>94.15 ± 28.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C$_{max}$ (ng/mL)</td>
<td>8.39 ± 2.89</td>
<td>7.00 ± 2.04</td>
<td>0.0114</td>
</tr>
<tr>
<td>C$_{min}$ (ng/mL)</td>
<td>4.66 ± 1.71</td>
<td>2.80 ± 0.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C$_{avg}$ (ng/mL)</td>
<td>5.93 ± 2.06</td>
<td>3.92 ± 1.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% fluctuation</td>
<td>64.72 ± 22.97</td>
<td>110.21 ± 28.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% swing</td>
<td>85.45 ± 37.62</td>
<td>158.53 ± 48.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T$_{max}$ (hr)*</td>
<td>8.00 (1 - 12)</td>
<td>2.00 (1 - 6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>C$<em>{max}$/C$</em>{min}$</td>
<td>1.85 ± 0.38</td>
<td>2.59 ± 0.48</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Median (min – max); Means ± SD displayed

Nigro et al, presented at AST/ESOT joint meeting 2012
This double-blind, double-dummy, multi-center study was conducted to establish the efficacy and safety of Envarsus tablets for prevention of allograft rejection in de novo adult kidney transplant recipients.

Primary efficacy was evaluated at Month 12 by a composite endpoint comprised acute rejection, graft loss, death or loss to follow-up with a pre-specified non-inferiority margin of 10%. Efficacy and safety outcomes were also evaluated at Month 24.
Tacrolimus Trough Level Achieved Per Total Daily Dose

Improved Absorption (Bioavailability) Confirmed with Envarsus

The difference between Envarsus and Prograf was statistically significant (p ≤ 0.02) at all time points, except week 3.

Budde K et al., AJT 2014 Oct 2. doi: 10.1111/ajt.12955
Calcineurin inhibitors and new onset of diabetes mellitus (NODM)
Results of an International, Randomized Trial Comparing Glucose Metabolism Disorders and Outcome with Cyclosporine Versus Tacrolimus (1)

DIRECT Study

702 assessed for eligibility

690 randomized

12 excluded*

339 allocated to CsA-ME
336 received CsA-ME
3 did not receive CsA-ME
- 2 not transplanted
- 1 not given study drug

1 lost to follow-up*
16 discontinued
(8 deaths, 8 consent withdrawal)

351 allocated to tacrolimus
346 received tacrolimus
5 did not receive tacrolimus
- 4 not transplanted
- 1 not given study drug

8 lost to follow-up*
11 discontinued
(8 deaths, 3 consent withdrawal)

*Reasons not recorded

Patient disposition. CsA-ME = cyclosporine microemulsion; ITT = intent-to-treat.

Vincenti F et al. AJT 2007;7(3): 1506-14
Results of an International, Randomized Trial Comparing Glucose Metabolism Disorders and Outcome with Cyclosporine Versus Tacrolimus (2)

Kaplan–Meier plot of **time to onset of first hypoglycemic treatment in the nondiabetic population**.

Vincenti F et al. AJT 2007;7(3): 1506-14
Results of an International, Randomized Trial Comparing Glucose Metabolism Disorders and Outcome with Cyclosporine Versus Tacrolimus (3)

Efficacy endpoints at month 6 posttransplant

<table>
<thead>
<tr>
<th></th>
<th>CsA-ME (n = 336)</th>
<th>Tacrolimus (n = 346)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR, graft loss or death</td>
<td>43 (12.8%)</td>
<td>34 (9.8%)</td>
<td>0.211</td>
</tr>
<tr>
<td>BPAR</td>
<td>34 (10.1%)</td>
<td>24 (6.9%)</td>
<td>0.132</td>
</tr>
<tr>
<td>Severity of rejection¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IA</td>
<td>15</td>
<td>9</td>
<td>Not done</td>
</tr>
<tr>
<td>Grade IB</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Grade IIA</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Grade IIB</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Treated rejection</td>
<td>50 (14.9%)</td>
<td>38 (11%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Antibody-treated rejection</td>
<td>11 (3.3%)</td>
<td>12 (3.5%)</td>
<td>0.888</td>
</tr>
<tr>
<td>Recurrent rejection</td>
<td>4 (1.2%)</td>
<td>3 (0.9%)</td>
<td>Not done</td>
</tr>
<tr>
<td>Graft loss</td>
<td>8 (2.4%)</td>
<td>10 (2.9%)</td>
<td>0.693</td>
</tr>
<tr>
<td>Graft loss due to rejection</td>
<td>0</td>
<td>3 (0.9%)</td>
<td>0.087</td>
</tr>
<tr>
<td>Death or graft loss</td>
<td>9 (2.7%)</td>
<td>13 (3.8%)</td>
<td>0.439</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3%)</td>
<td>3 (0.9%)</td>
<td>0.338</td>
</tr>
</tbody>
</table>

1.¹Banff classification (21).
2.²An additional seven CsA-ME patients and five tacrolimus patients died after discontinuation of study medication.

BPAR = biopsy-proven acute rejection.

Vincenti F et al. AJT 2007;7(3): 1506-14
BKV viruria and viremia rates according to the treatment arm.

(A) BKV viruria;
(B) BKV viruria above $7 \log_{10}$ geq/mL (high-level viruria);
(C) urine BKV loads in viruric patients;
(D) BKV viremia;
(E) BKV viremia above $4 \log_{10}$ geq/mL (high-level viremia);
(F) plasma BKV loads in viremic patients.

mTOR-inhibitors
(Sirolimus and Everolimus)
Rapamune Maintenance Regimen (Study 310)

Design

Sirolimus + CsA + Steroids

> 5 ng/mL

150-400 ng/mL

N=525

Patients with a history of malignancy within 5 years before transplantation, other than adequately treated BCC or SCC, were excluded.

Discontinued
Before randomization
n=95

SRL-CsA-ST
n=215

Sirolimus* (> 5 ng/mL)

CsA (50-150 ng/mL)

Steroids

3 months ± 2 weeks

Sirolimus*

(20-30 ng/mL ≤ 1 yr)

(15-25 ng/mL > 1 yr)

Steroids

CsA

Stopped
(25% per week)

SRL-ST
n=215

Patients with a history of malignancy other than adequately treated BCC or SCC, were excluded.

N=525

Sirolimus therapy in *de novo* KTx and *de novo* posttransplant malignancies (1)

**RMR study: On-therapy**

**A**

Kaplan-Meier plot of time to first skin carcinoma.

**B**

Cumulative number of skin carcinomas.

**RMR study: ITT**

**A**

Kaplan-Meier plot of time to first skin carcinoma.

**B**

Cumulative number of skin carcinomas.

**Analysis of any skin carcinoma.**

(A) Kaplan-Meier plot of time to first skin carcinoma.

(B) Cumulative number of skin carcinomas.

---

Campistol JM et al. JASN 2006;17:581-589
Sirolimus therapy in *de novo* KTx and *de novo* posttransplant malignancies (2)

Kaplan-Meier plots of time to **non-skin malignancies**.
(A) On-therapy.
(B) Intention-to-treat.
Sirolimus and secondary skin cancer prevention in KT patients

• Multicenter, prospective controlled study in maintenance KT patient on CNI-based immunosuppression having ≥1 cutaneous squamous cell carcinoma. remain on CNI (n=56)

  – Randomization to

  – Primary end-point: squamous cell carcinoma-free survival over 2 years.

• Results:

  – Recurrent SCC: 22% on SRL vs. 39% on CNI (median time 15 vs. 7 months); p=0.02 RR = 0.56 (0.32 – 0.98)

  – All de novo skin cancers: SRL: 47.6% vs. 70.5% (CNI); p=0.048

  – Graft function remained stable in both groups

Euvrard S et al., NEJM 2012; 367:329-39
Incidence of infections was evaluated in six studies. Everolimus with CNI sparing did not contribute to any more infections with an RR = 1.05 (95% CI [0.97, 1.13]; P = 0.2; heterogeneity, I² = 0%). Incidence of CMV infection was lower in CNI sparing group (RR 0.47; 95% CI [0.32, 0.70]; P = 0.0002; heterogeneity, I² = 61%);
Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving everolimus and reduce tacrolimus doses (1)

doi:10.1111/ajt.13327
Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving everolimus and reduce tacrolimus doses (2)

(A) Mean tacrolimus whole blood concentrations.

(B) Mean everolimus blood (whole) and mean mycophenolate acid (plasma) concentrations

Reduced incidence of cytomegalovirus infection in kidney transplant recipients receiving everolimus and reduce tacrolimus doses (3)

Cumulative incidence of CMV infection/disease during the 12 months of follow up

**Secondary endpoints**

<table>
<thead>
<tr>
<th></th>
<th>r-ATG/EVR (N=85)</th>
<th>BAS/EVR (N=102)</th>
<th>BAS/MPS (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure, N (%)</td>
<td>13 (15.3)</td>
<td>23 (22.6)</td>
<td>24 (23.8)</td>
</tr>
<tr>
<td>First biopsy confirmed acute rejection, N (%)</td>
<td>8 (9.4)</td>
<td>19 (18.6)</td>
<td>16 (15.8)</td>
</tr>
<tr>
<td>IA</td>
<td>1 (1.2)</td>
<td>5 (4.9)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>IB</td>
<td>5 (5.9)</td>
<td>7 (6.9)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>IIA</td>
<td>0</td>
<td>6 (5.9)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>IIB</td>
<td>0</td>
<td>1 (1.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Antibody-mediated changes</td>
<td>1 (1.2)</td>
<td>0</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Acute antibody-mediated rejection</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death, N (%)</td>
<td>3 (3.5)</td>
<td>5 (4.9)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>Graft loss, N (%)</td>
<td>1 (1.2)</td>
<td>3 (2.9)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Loss to follow up, N (%)</td>
<td>1 (1.2)</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Patient survival, (%)</td>
<td>96.5</td>
<td>95.1</td>
<td>96.0</td>
</tr>
<tr>
<td>Graft survival, (%)</td>
<td>95.3</td>
<td>93.1</td>
<td>89.1</td>
</tr>
<tr>
<td>Death-censored graft survival, (%)</td>
<td>98.8</td>
<td>97.1</td>
<td>93.1</td>
</tr>
<tr>
<td>First treated acute rejection, N (%)</td>
<td>19 (22.3)</td>
<td>35 (34.3)</td>
<td>29 (28.7)</td>
</tr>
<tr>
<td>Antibody treated rejection, N (%)</td>
<td>1 (1.2)</td>
<td>7 (6.9)</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Wound-healing complications, N (%)</td>
<td>20 (23.5)</td>
<td>35 (34.3)</td>
<td>23 (22.8)</td>
</tr>
<tr>
<td>DGF, N (%)</td>
<td>32 (47.0)</td>
<td>32 (48.5)</td>
<td>27 (41.5)</td>
</tr>
<tr>
<td>Duration of DGF, days (mean ± SD)</td>
<td>11.3 ± 5.3</td>
<td>14.7 ± 14.3</td>
<td>9.9 ± 5.8</td>
</tr>
<tr>
<td>Creatinine, mg/dL (mean ± SD)</td>
<td>1.4 ± 0.64</td>
<td>1.5 ± 0.5</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>eGFR, ml/min (mean ± SD)*</td>
<td>65.7 ± 21.8</td>
<td>60.6 ± 20.9</td>
<td>69.5 ± 21.5</td>
</tr>
<tr>
<td>Urine protein/creatinine ratio, (mean ± SD)</td>
<td>0.4 ± 0.7</td>
<td>0.4 ± 0.8</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td>Proteinuria &gt; 0.5 mg/L, N (%)</td>
<td>21 (26.5)</td>
<td>21 (22.8)</td>
<td>16 (18.0)</td>
</tr>
</tbody>
</table>

• ATG, antithymocyte globulin; BAS, basiliximab; EVR, everolimus; MPS, mycophenolate sodium.
• First treated acute rejection was defined as the first episode of acute rejection, confirmed or not by biopsy that was treated with either methylprednisolone or polyclonal antibody.
• *BAS/EVR vs. BAS/MPS, p = 0.016.
BELATACEPT
Belatacept blocks CD28:CD80/CD86 costimulation and prevents T cell activation

Compared with CTLA4-Ig, belatacept has:
- 4-fold higher avidity for CD86
- 2-fold higher avidity for CD80
- ~10-fold more potent inhibition of T-cell activation \textit{in-vitro}

- No cell division
- No cytokine production
- Anergy
- Apoptosis.
Population étudie: patients ayant reçu un greffon rénal issu de donneur vivant ou décédé à critères standards (SCD: BENEFIT) ou à critères élargis (BENEFIT-EXT).

**Transplantation**

- **Belatacept MI**
  - Jour 1: 10 mg/kg
  - 6 mois: 5 mg/kg toutes les 4 semaines

- **Belatacept LI**
  - Jour 1: 10 mg/kg
  - 6 mois: 5 mg/kg toutes les 4 semaines
  - **Régime approuvé**

- **CsA**
  - Jour 1: 150–300 ng/ml
  - 28: 100–250 ng/ml

**Points d’évaluation cliniques (mois)**

- Jour 1
- 5
- 14
- 28
- 42
- 56
- 70
- 84
- 112
- 140
- 168
- 12
- 24
- 36
- 84

**Perfusions de placebo**
- belatacept en aveugle jusqu’à 12 mois.
- Tous les patients ont reçu basiliximab en induction, mycophénolate mofétil et des corticoides.

CsA = cyclosporine A ; LI = moins intensif ; MI = plus intensif ; SCD = donneur à critères standard.
Belatacept and Long-Term Outcomes in Kidney Transplantation (1)

Number of patients who were enrolled, underwent randomization, and completed the study.

738 Patients were enrolled

666 Underwent randomization

219 Were assigned to belatacept M1
- Mo 0–3: 10 mg/kg on days 1 and 5
- and at wk 2, 4, 6, 8, 10, and 12
- Mo 4–6: 10 mg/kg at wk 16, 20, and 24
- Beyond mo 6: 5 mg/kg every 4 wk

226 Were assigned to belatacept L1
- Mo 0–1: 10 mg/kg on days 1 and 5
- and at wk 2 and 4
- Mo 2–3: 10 mg/kg at wk 8 and 12
- Beyond mo 3: 5 mg/kg every 4 wk

221 Were assigned to cyclosporine
- Initial daily dose: 4–10 mg/kg
- Mo 0–1: dose adjusted to
- 150–300 ng/ml
- Beyond mo 1: dose adjusted to
- 100–250 ng/ml

219 Underwent transplantation

226 Underwent transplantation

221 Underwent transplantation

219 Were treated

226 Were treated

221 Were treated

91 Discontinued study
- 39 Were ineligible for or declined LTE
- 14 withdrew consent
- 13 had adverse event
- 13 died
- 4 were lost to follow-up
- 2 were pregnant
- 1 had poor adherence or was nonadherent
- 5 had other reason

90 Discontinued study
- 34 were ineligible for or declined LTE
- 20 withdrew consent
- 11 had adverse event
- 11 died
- 4 were lost to follow-up
- 3 had lack of efficacy
- 1 was pregnant
- 1 had poor adherence or was nonadherent
- 1 had administrative reason
- 4 had other reason

123 Discontinued study
- 43 were ineligible for or declined LTE
- 23 died
- 22 withdrew consent
- 12 had adverse event
- 8 were lost to follow-up
- 6 had lack of efficacy
- 4 had poor adherence or were nonadherent
- 1 had administrative reason
- 6 had other reason

128 Completed 84-mo study

136 Completed 84-mo study

92 Completed 84-mo study

153 Could be evaluated at 84 mo

163 Could be evaluated at 84 mo

131 Could be evaluated at 84 mo
Patient and graft survival at 84th posttransplantation

Patient and graft survival at 84th posttransplantation

N à risque

Mois

0 6 12 18 24 30 36 42 48 54 60 66 72 78 84

Probabilité de survie

Mois 60

Valuer P  HR (95 % IC)
Bela MI par rapport à CsA 0,0100  0,521 (0,306, 0,889)
Bela LI par rapport à CsA 0,0045  0,477 (0,277, 0,819)

Mois 84

Valuer P  HR (95 % IC)
Bela MI par rapport à CsA 0,0225  0,573 (0,348, 0,946)
Bela LI par rapport à CsA 0,0210  0,570 (0,348, 0,935)

Bela = belatacept ; IC = intervalle de confiance ; CsA = ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.
Patient survival at 84th posttransplantation

<table>
<thead>
<tr>
<th>Mois 60</th>
<th>Moist 84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valeur P</td>
<td>HR (95 % IC)</td>
</tr>
<tr>
<td>Bela MI par rapport à CsA</td>
<td>0,0491</td>
</tr>
<tr>
<td>Bela LI par rapport à CsA</td>
<td>0,0248</td>
</tr>
</tbody>
</table>

Bela = belatacept ; IC = intervalle de confiance ; CsA = ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.
Graft survival at 84th posttransplantation

N à risque
Belatacept MI 219 212 208 206 204 202 199 153 151 149 146 142 135 131 128
Belatacept LI 226 220 218 216 213 209 204 165 161 159 152 151 142 139 137
CsA 221 208 206 202 199 197 186 137 123 117 112 107 102 100 92

Mois 60
<table>
<thead>
<tr>
<th></th>
<th>Mois 60</th>
<th>HR (95 % IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bela MI par rapport à CsA</td>
<td>0,1204</td>
<td>0,562 (0,257, 1,228)</td>
</tr>
<tr>
<td>Bela LI par rapport à CsA</td>
<td>0,0659</td>
<td>0,487 (0,217, 1,093)</td>
</tr>
</tbody>
</table>

Mois 84
<table>
<thead>
<tr>
<th></th>
<th>Mois 84</th>
<th>HR (95 % IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bela MI par rapport à CsA</td>
<td>0,1215</td>
<td>0,555 (0,254, 1,213)</td>
</tr>
<tr>
<td>Bela LI par rapport à CsA</td>
<td>0,1505</td>
<td>0,587 (0,275, 1,254)</td>
</tr>
</tbody>
</table>

Bela = belatacept ; IC = intervalle de confiance ; CsA = cyclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.
Belatacept and Long-Term Outcomes in Kidney Transplantation (2)

Glomerular filtration rate over the period from month 1 to month 84

Acute rejection rate over 84th months

<table>
<thead>
<tr>
<th>Degré Banff de rejet aigu*, n</th>
<th>Belatacept MI (N = 219)</th>
<th>Belatacept LI (N = 226)</th>
<th>CsA (N = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aigu léger (IA)</td>
<td>7 (3,2)</td>
<td>4 (1,8)</td>
<td>6 (2,7)</td>
</tr>
<tr>
<td>Aigu léger (IB)</td>
<td>3 (1,4)</td>
<td>8 (3,5)</td>
<td>7 (3,2)</td>
</tr>
<tr>
<td>Aigu modéré (IIA)</td>
<td>18 (8,2)</td>
<td>17 (7,5)</td>
<td>7 (3,2)</td>
</tr>
<tr>
<td>Aigu modéré (IIB)</td>
<td>22 (10,0)</td>
<td>10 (4,4)</td>
<td>3 (1,4)</td>
</tr>
<tr>
<td>Aigu sévère (III)</td>
<td>3 (1,4)</td>
<td>1 (0,4)</td>
<td>0 (0,0)</td>
</tr>
</tbody>
</table>

Valeur P    HR (95 % IC)
Belatacept MI par rapport à CsA 0,0001 2,649 (1,596, 4,397)
Belatacept LI par rapport à CsA 0,0302 1,905 (1,124, 3,232)

IC = Intervalle de confiance ; CsA = ciclosporine A ; HR = rapport de risque ; LI = moins intensif ; MI = plus intensif.

N à risque
Belatacept MI 219 154 147 144 140 137 136 128 127 125 122 117 111 108 105
Belatacept LI 226 168 164 162 160 157 155 149 144 142 137 135 130 125 122
CsA           221 130 167 156 147 141 135 123 115 110 106 101 96 94 83

Mois
Incidence of *de novo* DSAs

<table>
<thead>
<tr>
<th>DSA Specificity</th>
<th>Bela MI</th>
<th>Bela LI</th>
<th>CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>3</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Class I, n</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Class II, n</td>
<td>2</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Class I and II, n</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

95% CI
Belatacept MI: 0.28–3.95
Belatacept LI: 0.84–5.36
CsA: 7.34–15.91

CI=confidence interval; CsA=cyclosporine A; DSA=donor-specific antibody; LI=less intensive; MI=more intensive.
Thank you for your attention