Transplant drugs for the non-transplanting Nephrologist

Paul Trevillian
DNT Meeting
Cyprus Lakes
28/3/11
Transplant drugs (Maintenance not induction)

1. Immunosuppressives/immunomodulators
   - CNI’s (CSA and TAC)
   - Anti-Proliferatives:
     - Nucleic acid inhibitors (Mycophenolate, leflunomide)
     - mTor inhibitors (Sirolimus, Everolimus)
   - Glucocorticoids (Prednisone)
   - Co-stimulation blockers (Belatacept)

2. Monoclonal antibodies:
   - Anti-IL2R (basiliximab)
   - ATG (Thymoglobulin)
   - antiC5a (Eculuzimab)
   - Anti-CD52 (Campath)
   - Proteosome Inhitor (Bortezimib)
Transplant drugs (maintenance not induction)

3. Adjunctive Drugs.
   • CNI sparing agents
   • Lipid lowering
   • Ulcer prophylaxis
   • Bone metabolism
   • Mineral replacement
   • CMV prophylaxis
   • Antihypertensives

4. Switching strategies

5. “Horizon” drugs
   • JAK 3 inhibitors
   • PKC inhibitors
   • Monoclonals and biologicals
Clinical Scenario

• Mr. YP 57, has DD renal Tx (donor 55, cerebral haem.) and is returned to your care after uneventful 3 weeks at transplanting hospital.

  – YP has ESKD from **IgA nephropathy** and had a **previous transplant** from his mother which was lost after 12 yrs from “CAN”. Back on HDX for 2yrs
  
  – He has had previous blood transfusions, **peak PRA 36%**, current 20%
  
  – 8/14 HLA MM, T-, B- CDC XM, Luminex pos Class 1 and 2, but **no DSAb’s**
  
  – **FH diabetes** but GTT 2 yrs ago was normal, BMI = 31
  
  – Known **diverticulosis** and intermittent G-Oes reflux
  
  – **2 BCC’s and 2 SCC’s** removed in past.
  
  – CMV=D+/R+.
  
  – PTH = 170 pg/ml and was started on **Cinacalcet** 3 months before Tx
# Medication on Discharge

(= 44 tablets)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppression</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (Prograf)</td>
<td>po</td>
<td>4 mg</td>
<td>bd</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate Mofetil (Cellcept)</td>
<td>po</td>
<td>1000mg</td>
<td>bd</td>
<td></td>
</tr>
<tr>
<td>Prednisone (Sone)</td>
<td>po</td>
<td>30 mg</td>
<td>daily</td>
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<tr>
<td><strong>Calcineurin Sparing Medication</strong></td>
<td></td>
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<tr>
<td>Diltiazem (Cardizem)</td>
<td>po</td>
<td>180 mg</td>
<td>daily</td>
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<td><strong>Anti-microbial prophylaxis</strong></td>
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<tr>
<td>Valgancyclovir (Valcyte)</td>
<td>po</td>
<td>450mg</td>
<td>daily</td>
<td>Cease at 3 months</td>
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<td>Co-Trimoxazole (Resprim)</td>
<td>po</td>
<td>400/80mg</td>
<td>daily</td>
<td>Cease at 6 months</td>
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<td><strong>Ulcer Prophylaxis</strong></td>
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<td>Ranitidine (Zantac)</td>
<td>po</td>
<td>150 mg</td>
<td>bd</td>
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<td><strong>Bone Metabolism</strong></td>
<td></td>
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<tr>
<td>Calcitriol (Rocaltrol)</td>
<td>po</td>
<td>0.5 µg</td>
<td>twice weekly</td>
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<tr>
<td>Calcium carbonate (Caltrate)</td>
<td>po</td>
<td>600 mg</td>
<td>daily</td>
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<tr>
<td>Cinacalcet (Sensipar)</td>
<td>po</td>
<td>30 mg</td>
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<tr>
<td><strong>Mineral Replacement</strong></td>
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<td>Sodium Bicarbonate (Sodibic)</td>
<td>po</td>
<td>1680mg</td>
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<td>Sod. Phosphate (Sandiphos)</td>
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<td>Mag. Aspartate (Magmin)</td>
<td>po</td>
<td>500 mg</td>
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<tr>
<td><strong>Antihypertensives</strong></td>
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<td>Prazosin (Pressin)</td>
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<td>4mg</td>
<td>tds</td>
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<td>Metoprolol (Minax)</td>
<td>po</td>
<td>50 mg</td>
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<td>Aspirin (Astrix)</td>
<td>po</td>
<td>100 mg</td>
<td>daily</td>
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<tr>
<td><strong>Lipid lowering</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rosuvastatin (Crestor)</td>
<td>po</td>
<td>10 mg</td>
<td>daily</td>
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**Lab. Results**

<p>| | |</p>
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<tbody>
<tr>
<td>Hb</td>
<td>113</td>
</tr>
<tr>
<td>WCC</td>
<td>9.8</td>
</tr>
<tr>
<td>Plat</td>
<td>170</td>
</tr>
<tr>
<td>Creat</td>
<td>165</td>
</tr>
<tr>
<td>TAC</td>
<td>16.5</td>
</tr>
<tr>
<td>f BSL</td>
<td>7.6</td>
</tr>
</tbody>
</table>

**o/e:** Tremor ++

**Oedema +**

**Wt:** 98kg

**BP:** 160/95
## Immunosuppression – Which CNI?

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<td>po</td>
<td>30 mg</td>
<td>daily</td>
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</tbody>
</table>
## Calcineurin inhibitors – CSA vs TAC

<table>
<thead>
<tr>
<th>Properties</th>
<th>CSA</th>
<th>TAC</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Anti-rejection</td>
<td>++</td>
<td>++++</td>
<td>SAR = 30% vs 0% On 3 mo. PTBx Less AR, Less graft loss, Cochrane Higher MMF levels</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Ease of use</td>
<td>++</td>
<td>++++</td>
<td>C2 vs C0 levels Once daily preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cosmetic</td>
<td>+++</td>
<td>+</td>
<td>Hirsutism, gum hypertrophy</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>++</td>
<td>++++</td>
<td>TAC 2-4 x diabetes risk. Better CVS risk profile??</td>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BKV</td>
<td>+/-</td>
<td>+++</td>
<td>CSA inhibits BKV in vitro</td>
</tr>
<tr>
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<tr>
<td>Diarrhoea, CNS</td>
<td>+/-</td>
<td>+++</td>
<td>TAC assoc’d with V&amp;D Potentiates MMF CSA more constipation?</td>
</tr>
<tr>
<td>(Tremor, headache)</td>
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</tbody>
</table>

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C2 vs C0 levels
Once daily preparation

BKV +/- +++ CSA inhibits BKV in vitro

TAC assoc’d with V&D Potentiates MMF CSA more constipation?
Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients

Webster AC, Taylor RRS, Chapman JR, Craig JC  Cochrane review 2005

Authors’ conclusions
Tacrolimus is superior to cyclosporin in improving graft survival and preventing acute rejection after kidney transplantation, but increases post-transplant diabetes, neurological and gastrointestinal side effects. Treating 100 recipients with tacrolimus instead of cyclosporin would avoid 12 suffering acute rejection, two losing their graft but cause an extra five to become insulin-requiring diabetics.

There was insufficient information to assess the cost of tacrolimus versus cyclosporin, and there was a general failure to consider global quality of life (QOL) for transplant recipients which may inform our understanding of patient preference and compliance.

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)

2.2.1: We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)
Australian Grafts at time of TX

percent


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What do we do?

“Standard”, low risk transplants (PRA <10, XM –ve, Luminex, neg)….. **CSA**
Low/moderate risk with abnormal GTT .................................................. **CSA**
Young recipients < 30 (high responders + cosmetic issues).............. **TAC**
Retransplants................................................................................................**TAC**
ABOi’s........................................................................................................... **TAC**
Sensitised (PRA > 10%, DSAb’s, XM +)................................................. **TAC**

Calcineurin inhibitors – CSA vs TAC
Tacrolimus TDM

- **Monitor trough (C₀) – CARI** (even though C3 and SS-AUC are better for total exposure)

### Australian Grafts

**Maintenance Tacrolimus dose**

<table>
<thead>
<tr>
<th>Year</th>
<th>Induction</th>
<th>6 months</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td>1999</td>
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<td>2000</td>
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<td>2007</td>
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<td>2008</td>
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</tbody>
</table>

ANZDATA 2011
Australian Grafts
Maintenance CYA Dose

Transplant year

Maintenance CYA dose, mg/kg/day

Induction CYA dose, mg/kg/day

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Calcineurin Sparing Medication

Diltiazem (Cardizem)  po  180 mg  daily


Associations between use of cyclosporine-sparing agents and outcome in kidney transplant recipients

Stephen P. McDonald and Graeme R. Russ

ANZDATA Registry, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia

- **3913** kidney transplants between 1 April 1993 and 30 March 2001.
- 57% received CsSpA, more commonly in larger units
- Delayed graft function significantly less common with CsSpA (OR 0.61, \( P < 0.0001 \)).
Q. Should I change to modified-release TAC (Advagraf)

- Better adherence
- Cost neutral
- Concern re reduced TAC exposure on recommended 1:1 dose substitution?? Two studies:


**De novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels.**


**CONCLUSION:** It was necessary to use up to a 50% higher dose of Advagraf than Prograf to achieve similar trough levels during the first 6 months.

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Transplantation: 15 March 2011 - Volume 91 - Issue 5 - pp 566-569

**Conversion From Prograf to Advagraf Among Kidney Transplant Recipients Results in Sustained Decrease in Tacrolimus Exposure**

_Hougardy, Jean-Michel1,3; Broeders, Nilufer1; Kianda, Mireille1; Massart, Annick1; Madhoun, Philippe1; Le Moine, Alain1; Hoang, Anh-Dung1; Mikhalski, Dimitri1; Wissing, Karl M.1,2; Abramowicz, Daniel1_

**CONCLUSION:** At 6 months, 35% of patients experienced a decrease in trough levels of more than 30%.

In neither case was there any difference in AR or graft outcome!
Q. When should I consider switching TAC to CsA?

- BK viraemia
- BK nephropathy
- NODAT?
  - Switching from tacrolimus to cyclosporine has been reported to lead to resolution of NODAT in a significant minority of patients and better glycaemic control overall in two single centre studies of kidney [18] and liver [19] transplant recipients. (S. Chadban)

- Thrombotic microangiopathy??
Anti-proliferative agent

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<td>bd</td>
<td></td>
</tr>
<tr>
<td>Prednisone (Sone)</td>
<td>po</td>
<td>30 mg</td>
<td>daily</td>
<td></td>
</tr>
</tbody>
</table>
Suggested possible indications for MPA monitoring:

- an acute or chronic deterioration in graft function
- onset or change of renal, liver, or bowel (dys)function (including diarrhea, which may be of infective origin rather than being due to MPA)
- a substantial change in serum albumin concentration
- a clinically indicated change of CNI type or dosing
- use of MMF in primary therapy (without CNI) or monotherapy
- a change in the exposure to other interacting medications, in particular oral antibiotics and rifampicin

Mycophenolate – TDM or not?

- Mycophenolate mofetil has conventionally been administered at a fixed dose without routinely monitoring MPA blood levels.

- The proposed therapeutic window of the MPA AUC0–12 (30–60 ug·h/mL) is restricted to the early posttransplant period and when MMF is used in combination with CsA.

- In general, MPA C0 1.0–3.5 mg/L correlates with MPA AUC0–12 (30–60 ug·h/mL) in patients treated with CsA.

5.2: We suggest monitoring MMF levels. (2D)
Mycophenolate TDM – what we do:

- C0 levels in first weeks prn - for adequacy (>1.0)
- Sparse sample AUC at 1 month (C0, C0.5, C2)
- Repeat SS-AUC prn if Mycophenolate side effects (often after dose reduction)
Mycophenolate/CNI interaction

- CsA decreases MPA exposure by about 40% cf. TAC (CsA blocks entero-hepatic circulation of MPAG preventing the “second peak” of MPA absorption)

- CNI’s initially commonly cause some liver dysfunction making it hard to achieve therapeutic MPA levels

- Hence interest in intensified MPA induction especially with CsA
Possible advantages of EC-MPS over MMF

• Less Gi side-effects (in subgroups only)
• Ability to use intensified induction regimen
• Less interaction with PPI’s
• Less AR in one study attributed to better MPA levels
MMF (Cellcept) vs. Mycophenolate EC (Myfortic)  
**GI side effects**


**Langone AJ, Chan L, Bolin P, Cooper M.**  
Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN, USA.  
anthony.langone@vanderbilt.edu

- Results. Three hundred ninety-six patients (EC-MPS group: n=199; MMF group: n=197) were included.

- A greater proportion of EC-MPS patients (62%) reached the primary efficacy outcome compared with MMF patients (55%); however, the difference was **not statistically significant** (P=0.15).
MYC-EC - Less interaction with PPI’s

Following a single oral dose of MMF 1000 mg or EC-MPS 769 mg (equivalent to 720 mg MPA)

MPA (µg/mL)

<table>
<thead>
<tr>
<th>MPA (µg/mL)</th>
<th>Time (h)</th>
</tr>
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<tbody>
<tr>
<td>35</td>
<td>0</td>
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<tr>
<td>30</td>
<td>4</td>
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<tr>
<td>20</td>
<td>8</td>
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<td>10</td>
<td>12</td>
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<tr>
<td>0</td>
<td>0</td>
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</tbody>
</table>

MMF

MMF / PPI

EC-MPS

EC-MPS / PPI

Plasma concentration-time course of MPA following single oral dose of MMF 1000 mg with or without 40 mg PPI (n=12)

Plasma concentration-time course of MPA following single oral dose of EC-MPS 720 mg with or without 40 mg PPI (n=12)


MPA: mycophenolic acid; PPI, proton pump inhibitor;
EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil
Australian Grafts

Anti-Proliferatives at 1 year post TX

ANZDATA 2011

17%
Mycophenolate - Strategies for Diarrhoea

**Acute:**
- Exclude infection
- **Reduce &/or redistribute dose**
- Check MMF level
- Consider change to Myfortic
- Check TAC level

**Chronic:**
- Exclude infection
- Check MMF level
- **Duodenal villous atrophy**
- Crohn’s like IBD
- Graft vs host
Mycophenolate - Strategies for Cytopenias

**Neutropenia:**
- Exclude CMV
- Reduce &/or redistribute MYC dose
- Stop MYC and increase or re-introduce steroid
- Consider ceasing valgan and co-trimoxazole
- *When to go for the G-CSF??*

**Anaemia:**
- 30% will remain anaemic long term (Hb worse than non-transplant pts with same GFR)
- These pts may benefit from EPO
- Do MMF levels (reduction in dose??)
- **PRCA = Parvovirus**
## Corticosteroid

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</table>
Adjunctive Drugs – some important interactions

- Ulcer prophylaxis
- Lipid lowering
- Bone metabolism
- Mineral replacement
potential adverse effects of long-term proton pump inhibitor use that have generated the greatest concern:

B(12) deficiency
iron deficiency
hypomagnesemia;
increased susceptibility to pneumonia
enteric infections
fractures
hypergastrinemia and cancer
drug interactions
birth defects

Those at increased risk from long-term ppi therapy:

Elderly,
malnourished,
immune-compromised,
chronically ill,
and osteoporotic patients
• The potential for drug interactions is thought to be the greatest with omeprazole and esomeprazole. Although rabeprazole is partly metabolized by CYP2C19 and CYP3A4, the major metabolic pathway is non-enzymatic.

• Therefore, it is thought that rabeprazole may exhibit a lower risk for pharmacological interactions and be less susceptible to inter-individual genetic variations in CYP2C19 and CYP3A4.11
We report two cases of hypomagnesemic hypoparathyroidism associated with the use of proton-pump inhibitors, in which patients presented with carpopedal spasm in association with severe hypomagnesemia and hypocalcemia without an appropriate increase in the level of parathyroid hormone.
• **Ranitidine is excreted via the kidneys mainly as unchanged drug**
  and in minor amounts as the N-oxide, S-oxide and desmethyl metabolites

<table>
<thead>
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<td>Ranitidine (Zantac)</td>
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</table>

What we do:

- If patients not currently symptomatic or taking a ppi -> use **Ranitidine**
- Cease after 6 months (after Pred withdrawal)
- If taking ppi or recent symptoms of GORD -> **Rabeprazole**
Lipid lowering

<table>
<thead>
<tr>
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</table>
Two Statins are hydrophilic, only partly metabolised and negligibly by the Cytochrome P 450 3A 4 enzyme – hence do not affect CNI levels

- **Pravastatin** is administered as an **acid** and is **hydrophilic** with 47% of administered drug appearing in urine.
- Most of remainder is either **sulphated** or degraded by stomach acid.
- Its degradation by CYP 450 3A is **1000x** less than Lovastatin

- **Rosuvastatin** is not extensively metabolised, (Approximately 10%, principally by CYP 450 2C9).
- Drugs (eg. Cyclosporin) that antagonize organic anion transporter protein 1B1-mediated hepatic uptake are more likely to interact with this statin.
- **When Cyclosporin is used in conjunction with Rosuvastatin at 10mg /day in cardiac transplant patients it increased blood Rosuvastatin 7.1 fold**

American Journal of Cardiovascular Drugs: 1 February 2010 - Volume 10 - Issue 1 - pp 11-28
Review Article
Rosuvastatin-Associated Adverse Effects and Drug-Drug Interactions in the Clinical Setting of Dyslipidemia
Kostapanos, Michael S.; Milionis, Haralampos J.; Elisaf, Moses S.
The drug of first choice for reducing LDL-C is a statin. **Doses of statins usually need to be reduced by approximately 50%** in patients treated with CsA, and probably also in patients treated with Tacrolimus (although fewer data are available).

**What we do:**

- **Pravastatin** – Safest, introduce at lowest dose. Use up to 80mg

- **Rosuvastatin** – the most potent statin, some lowering of TG’s. We don’t exceed 10 mg/day with TAC (company PI says don’t exceed 5 mg/day with CsA)

- Rarely if ever use **fibrates**
• Calcitriol
  – To maintain PTH suppression
  – Has some immunomodulatory properties
  – Hypercalcaemia frequently limits use

• Cinacalcet
  – Reduces GFR ? by reducing PTH and renal blood flow. Appears to be reversible
  – Not listed PBS in Australia for patients with functioning transplant

<table>
<thead>
<tr>
<th>Bone Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcitriol (Rocaltrol)</strong></td>
</tr>
<tr>
<td>Calcium carbonate (Caltrate)</td>
</tr>
<tr>
<td>Cinacalcet (Sensipar)</td>
</tr>
</tbody>
</table>

**Original Paper**

*Kidney Blood Press Res 2011;34:97-103*

**Renal Function in Patients Treated with Cinacalcet for Persistent Hyperparathyroidism after Kidney Transplantation**

Jana Henschkowskia, b, Heike A. Bischoff-Ferraria, b, Rudolf P. Wüthrichc, Andreas L. Serrac

Meta-analysis of 8 papers
<table>
<thead>
<tr>
<th>Mineral Replacement</th>
<th>po</th>
<th>1680mg</th>
<th>tds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Bicarbonate (Sodibic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Phosphate (Sandiphos)</td>
<td></td>
<td>500mg</td>
<td>bd</td>
</tr>
<tr>
<td>Magnesium aspartate (Magmin)</td>
<td></td>
<td>500 mg</td>
<td>bd</td>
</tr>
</tbody>
</table>

- How much for how long?
- Burden of Tablets versus benefit?

What we do:
- “full” replacement doses for 4-6 months
- then look to minimise
Mr. Y.P. is now under your care and doing well. What IS switch would you consider and why?

Considerations

- Already has skin cancers
- Appears to be developing NODAT
- Sub-optimal GFR
- Increased CVS risk
- Moderate/High immunological risk
Switch/withdraw Options

If high immunological risk

- **No change**
- **CNI withdrawal**
  - SRL / EVL
    - Anti-cancer?
    - Better GFR
  - Belatacept
    - Better CVS

Low immunological risk

- **MMF/MYC withdrawal**
  - AZA
    - Cheaper
- **PRED withdrawal**
  - Better CVS bones
  - Leflunomide
    - BKV
Steroid Withdrawal – the evidence

A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation.

Pascual J, Galeano C, Royuela A, Zamora J.


CONCLUSIONS: SW after 3 to 6 months of kidney transplantation is associated with increased rates of acute rejection only if CsA is used but not with tacrolimus. Graft fn and survival remain stable up to 3 years after transplantation, the longest follow-up reported.

Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis.

Knight SR, Morris PJ.

Transplantation. 2010 Jan 15;89(1)1-14.

CONCLUSION: Despite an increase in the risk of AR with SAW protocols, there is only a small effect on graft function with no measurable effect on graft or patient survival. There are significant benefits in cardiovascular risk profiles after SAW. SAW protocols would seem justified with current immunosuppressive protocols in low-risk recipients.

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)
Steroid withdrawal – what we do:

Withdraw from 3 months -> 6 months in all recipients at low immunological risk i.e.

- No previous graft
- No early rejection episodes
  - Except possibly early fully reversed ACR
- No subclinical rejection on 3/12 protocol biopsy
- PRA< 50% (Since 2005 - no DSAb on luminex)
Australian Grafts
CNI Free

Transplant year

Induction 1 year 3 years 5 years
Australian Grafts
mTOR inhibitors

Transplant year

Percentage on mTOR Inhibitors

- Induction
- 1 year
- 3 years
mTOR inhibitors

A plaque commemorating the discovery of sirolimus on Easter Island, near Rano Kau.

Lifespan extension in mice

Sirolimus

Everolimus
CNI Withdrawal – who can switch to mTORi?

Multiple studies with variable time points and variable definitions of who to switch.
Commonly:
- Low Immunological risk (various def'ns)
- eGFR >40
- Proteinuria < 800mg/d (<300mg/d?)

Side effects include refractory oedema
Q. Switch CNI to m-Tori - what is optimal time?

Switch too early:
- Delayed wound healing
- Lymphocele
- Worse DGF
- Potentiation of CNI toxicity
- Higher acute rejection rates

Switch too late:
- Lose benefit on GFR of CNI withdrawal
Q. Switch CNI to m-Tori - what is optimal time?

Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial

Lancet 2011; 377: 837–47

Rates of biopsy-proven acute rejection were higher in the everolimus group (15 [10%] of 154 vs five [3%] of 146; p=0·036),

Everolimus group also had:
- higher mean lipid concentrations
- slightly increased urinary protein excretion
- lower haemoglobin concentrations
- thrombocytopenia
- aphthous stomatitis,
- diarrhoea
- BUT nearly 10 ml/min better GFR
Mr Y.P.

You assess him to have:

- **moderate immunological risk**
- **high skin cancer risk**
- **high NODAT risk**
- mod/high CVS risk
- Risk of recurrent GN

Therefore:

- You minimise PRED to 7.5 mg/day over 3 months and continue indefinitely
- After 3 month protocol biopsy proves negative for Subclinical AR you minimise TAC but don’t stop it altogether
- You change MMF to mTORi at 4.5 months
- You add in low dose Neotigason (10mg/d) at 6 months ??

**Maintenance drugs**

- TAC MR 2mg daily (C0 = 3.1)
- EVL 0.5 mg bd (C0 = 6.2)
- PRED 7.5 mg/d
- Diltiazem 180mg
- Irbesarten 150mg
- Sodibic 840mg bd
- Aspirin ec 100mg
- Rosuvastatin 10mg = 10 tablets
In conclusion, although kidney transplant patients converted from CsA to sirolimus showed significant improvement in renal function, we found no difference of IF on 1-year biopsies.

Table 2: Interstitial fibrosis (IF) by treatment group expressed as percentage and grade

<table>
<thead>
<tr>
<th>Intent to treat</th>
<th>N</th>
<th>Grade I (% patients)</th>
<th>Grade II (% patients)</th>
<th>Grade III (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>60</td>
<td>48.3%</td>
<td>45.0%</td>
<td>6.7%</td>
</tr>
<tr>
<td>CsA</td>
<td>61</td>
<td>44.3%</td>
<td>45.0%</td>
<td>9.9%</td>
</tr>
<tr>
<td>On treatment</td>
<td>111</td>
<td>50.9%</td>
<td>43.4%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>53</td>
<td>46.6%</td>
<td>44.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>CsA</td>
<td>58</td>
<td>27.2 ± 16.1</td>
<td>46.6%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Continuous values are expressed as mean ± SD.
Belatacept (LEA 29Y)

- Fusion protein  CTLA4-Ig
- Inhibitor of co-stimulation  blocks binding of CD80 (B7-1) and CD86 (B7-2) to CD28 permitting a negative signal 2 stimulus between professional APC’s and naive T-cells

- Thought it would induce tolerance but not so
- Injectable preparation
Belatacept vs Cyclosporine in Kidney Transplant Recipients: BENEFIT Study: 2-Yr Outcomes

Christian Larsen, Josep Grinyó, Bernard Charpentier, José Medina Pestana, Nassim Kamar, Yves Vanrenterghem, Chen-Sheng Lin, Greg Di Russo, Pushkal Garg, Flavio Vincenti

ATC 2010
Randomization

Primary clinical endpoints

6 months

12 months

24 months

36 months

Belatacept MI*

10 mg/kg

5 mg/kg every 4 weeks

DAY 1 5 14 28 42 56 70 84 112 140 168

Belatacept LI*

10 mg/kg

5 mg/kg every 4 weeks

DAY 1 5 14 28 56 84 112

Cyclosporine*

150–300 ng/ml

100–250 ng/ml

DAY 1 28

*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids

Only CsA patients: T-cell depleting agents permitted for anticipated DGF

LI = less intensive; MI = more intensive.
## Safety Profile of Belatacept in Kidney Transplant Recipients from a Pooled Analysis of Phase II & Phase III Studies


<table>
<thead>
<tr>
<th>Study Type</th>
<th>Belatacept MI n = 477</th>
<th>Belatacept LI n = 472</th>
<th>CsA n = 476</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II Study</td>
<td>74</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>BENEFIT Study</td>
<td>219</td>
<td>226</td>
<td>221</td>
</tr>
<tr>
<td>BENEFIT-EXT Study</td>
<td>184</td>
<td>175</td>
<td>184</td>
</tr>
</tbody>
</table>
Adjudicated Causes of Death

- **Belatacept MI**
  - n = 477
  - Unknown: 3
  - Other: 2
  - Malignancy: 3
  - Infection: 12
  - Cardiovascular: 13

- **Belatacept LI**
  - n = 472
  - Unknown: 4
  - Other: 1
  - Malignancy: 3
  - Infection: 5
  - Cardiovascular: 10

- **CsA**
  - n = 476
  - Unknown: 6
  - Other: 2
  - Malignancy: 15
  - Infection: 12
  - Cardiovascular: 35
Current Belatacept trial protocols have now been modified to enroll EBV sero-positive patients only. (excludes many children)
1209 patients were randomized.

Mean systolic blood pressure was 6 to 9 mm Hg lower and mean diastolic blood pressure was 3 to 4 mm Hg lower in the MI and LI groups versus CsA.

Non-HDL cholesterol was lower in the belatacept groups versus CsA.

Serum triglycerides were lower in the belatacept groups versus CsA.

NODAT occurred less often in the belatacept groups versus CsA.

CONCLUSIONS.: At month 12, belatacept regimens were associated with better cardiovascular and metabolic risk profiles.
No ECD’s
Methyl pred to day 4
Thymo 1.5mg/kg
Ours appears to be the first regimen to show acceptable immunosuppression while avoiding CNIs from the time of transplant and eliminating corticosteroids after 5 days.
GUIDELINES
(Include recommendations based on level I or II evidence)

- C. In donor/recipient subgroups, prophylaxis for CMV disease is indicated for D+ and R+/- and D-/R+ on the pre-transplant CMV antibody assay. (Level II evidence)

- D. In donor/recipient subgroups, prophylactic treatment for CMV disease is not indicated for D -ve and R – ve on the pre-transplant CMV IgG antibody assay. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE
(Suggestions are based on Level III and IV evidence)

- Duration of therapy: Most trials had duration of prophylaxis of 90 days. In D+/R- 6-months prophylaxis reduces CMV disease and infection more than 3-months.

- Cost-effectiveness: In D+/R- recipients 6-months compared to 3-months prophylaxis was cost-effective in reducing CMV infection and disease.

- Prophylaxis is also indicated when using T cell depleting antibody (one RCT)

Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study.

Mr Y.P.

You assess him to have:

- moderate immunological risk
- high skin cancer risk
- high NODAT risk
- mod/high CVS risk
- Risk of recurrent GN

Therefore:

- You minimise PRED to 7.5 mg/day over 3 months and continue indefinitely
- After 3 month protocol biopsy negative for Subclinical AR you minimise TAC but don’t stop it altogether
- You change MMF to EVL at 4.5 months
- You add in low dose Neotigason (10mg/d) at 6 months

Maintenance I.S. = TAC 1mg bd (C0 = 3.1)
EVL 0.5 mg bd (C0 = 6.2)
PRED 7.5 mg/d
Personal Viewpoint

IMPACT Trial Results Should Not Change Current Standard of Care of 100 Days for Cytomegalovirus Prophylaxis

A. C. Kalil\textsuperscript{a,\*}, J. Sun\textsuperscript{b} and D. F. Florescu\textsuperscript{a}

\textsuperscript{a}Infectious Diseases Division, University of Nebraska Medical Center, Omaha, NE
\textsuperscript{b}National Institutes of Health, Bethesda, MD
\*Corresponding author: Andre Kalil, akalil@unmc.edu

- In summary, based on the multiple issues of study design, execution and statistical analysis, the IMPACT trial results do not have the strength of evidence to change the current clinical practice of 100-day CMV prophylaxis for high risk kidney recipients.

- Based on all available evidence, we consider that another clinical trial to test 200-day CMV prophylaxis is not necessary.
The evidence – I.S. and NODAT

Editorial Review

New-onset diabetes after transplantation—should it be a factor in choosing an immunosuppressant regimen for kidney transplant recipients?

Steven Chadban


- Steroid dose reduction may lead to some improvement in glycaemic control; however complete withdrawal appears to provide no significant metabolic benefits over low-dose maintenance of 5 mg/day of prednisolone [14] and may incur an increased risk of graft loss [15].

- Tacrolimus withdrawal may lead to improved glucose tolerance [16]; however, substitution with rapamycin does not [17].

- Switching from tacrolimus to cyclosporine has been reported to lead to resolution of NODAT in a significant minority of patients and better glycaemic control overall in two single centre studies of kidney [18] and liver [19] transplant recipients.

- What is likely to be of most benefit, however, is prevention.