

## Pharmacology Switch Therapy: Evidence or Voodoo??

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## Objectives

- Evaluate key factors of why patients get switched from one therapy to another
- Describe how to switch various therapies
  - MMF/MPA to azathioprine
  - Cellcept to Myfortic
  - Sirolimus to Calcineurin Inhibitor
  - Calcineurin Inhibitor to Sirolimus
  - PO to IV conversion for CNI's



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Why would you switch a  
patient's immunosuppressant  
regimen?



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**Switching therapies can be risky business**

- **If it's not broke, don't fix it...**
  - Providers can be reluctant to change a patient that has been stable on a regimen for months or years
  - Often patients can be maintained on one regimen life-long
- **But, what if your patient is experiencing toxicities?**




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**Potential Reasons for a Switch**

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| <ul style="list-style-type: none"> <li>• <b>Tacrolimus</b> <ul style="list-style-type: none"> <li>– Headaches/ tremors               <ul style="list-style-type: none"> <li>• Regardless of trough level</li> </ul> </li> <li>– Alopecia</li> <li>– Renal insufficiency/ CNI toxicity</li> <li>– BK virus/ other viruses?</li> <li>– Cancer</li> <li>– Post-Tx Diabetes Mellitus</li> <li>– General "intolerance"</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• <b>Cyclosporine</b> <ul style="list-style-type: none"> <li>– Rejection</li> <li>– Gingival Hyperplasia</li> <li>– Hirsutism</li> <li>– Renal Insufficiency/ CNI toxicity</li> <li>– Cancer</li> <li>– Hypertension</li> <li>– General "intolerance"</li> </ul> </li> </ul> |
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**Potential Reasons for a Switch**

**Sirolimus (Rapamune)**

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|---|--|
| <ul style="list-style-type: none"> <li>• Peripheral edema</li> <li>• Diarrhea</li> <li>• Proteinuria</li> <li>• Pulmonary fibrosis/ other issues</li> </ul> | <ul style="list-style-type: none"> <li>• Upcoming surgery</li> <li>• Unexpected surgery</li> <li>• General "Intolerance"</li> <li>• Insurance issues?</li> </ul> |
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### Potential Reasons for a Switch

#### Cellcept (MMF) or Myfortic (MPA)

- Diarrhea
- Consistently low WBC
- General intolerance
- Intubated
- Insurance issues?




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Is there evidence to support how to switch between the different immunosuppressant agents...

Or is it all Voodoo??




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### VOODOO (Mostly)

- Each provider has a different opinion on how to switch therapies
  - Right or wrong??
  - Checking levels makes it relatively easy
  - Put patients at risk of rejection
    - Good patient teaching/understanding is key
  - Patient safety primary concern
- “There is more than one way to skin a cat”




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## Recommendations

- The “Vanderbilt” Way
- A quick poll of other centers
- What is your method??



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## Cellcept/ Myfortic → Azathioprine



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## Cellcept/ Myfortic → Azathioprine

- Start Imuran (azathioprine) at 1-3 mg/kg/day
  - 3 - 5 mg/kg/day if early after tx?
  - 1 - 2 mg/kg/day if later
- Stop MMF/MPA after AM dose and start Imuran at bedtime (or vice versa)
- Azathioprine parent compound half-life
  - 3 hours
  - Plus metabolite half lives

Ducoux, D et al. *Transpl Int* 2005;15:387-392



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**Cellcept → Myfortic Switch**



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**Cellcept → Myfortic Switch**

- Most well studied with respect to equipotent doses
- Cellcept 250mg cap = Myfortic 180mg tab
- Cellcept 500mg tab = Myfortic 360mg tab



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**Sirolimus → CNi Switch Method**



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**Sirolimus → CNI Switch Method**

- **Easier conversion due to sirolimus drug properties**
  - Half life approximately 60 hours
- **Stop the sirolimus and start the CNI the next day**
  - Check a CNI level in 3-7 days
  - Usually Prograf 2 – 4mg twice daily to start
- **Similar methodology used at various centers**
  - Used most often for surgery/wound healing issues



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**CNI → Sirolimus Switch Method**



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**CNI → Sirolimus Switch Method**

- **Varying responses from nephrologists, cardiologists, pulmonologists, and other centers**
  - Load Sirolimus?
  - Start sirolimus at a standard dose?
  - When should we stop the CNI?
- **More difficult conversion because of Sirolimus drug properties**
  - Steady state concentration: 10-14 days
- **Contraindicated early post-op period**
  - Liver and lung transplant



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### CNi → Sirolimus Switch Method

- **LOAD method**
  - 2 - 4 days of a higher dose, then decrease to lower dose
    - Example: Sirolimus 10mg x 3 days, then 2mg daily
    - Example: Sirolimus 6mg, then 4mg, then 2mg daily
    - Example: Start Sirolimus 4mg, then 2mg daily
  - Some centers use a higher dose adjustment for African American patients



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### CNi → Sirolimus Switch Method

- **NO Loading Method**
  - **Vanderbilt**
    - Lung: Keep CNi on board, start SRL 2mg and check level in 10 days, if goal, then lower or stop CNi
    - Liver: No load dose, no overlap, start at 2mg qd
    - Renal: Various
    - Heart: No load, start sirolimus 2mg qd, overlap
  - Some centers determine if patient is high or low risk
    - Low risk: Cut the CNi to 50% of dose
    - High risk: Keep the CNi dose the same



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### CNi → Sirolimus Switch Method

- **NO Loading Method**
  - **Other protocols**
    - Start sirolimus at 1-3mg and continue CNi at full dose until sirolimus level at goal
      - \*or\*
    - Introduce sirolimus at 1mg daily and keep CNi at full dose
      - Check SRL level in 10-14 days
      - If (-), increase SRL 2mg daily, with no change in CNi
      - Continue this method until goal SRL
      - Stop CNi when SRL at goal



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**RCT of Late Conversion from CNi based to Sirolimus-Based Immunosuppression in Liver Transplant Recipients w/ Impaired Renal Function**

- **Adult liver transplant pts > 6 months post-op**
  - **Included:** GFR < 65mls/min on CNi therapy
  - **Excluded:** Pts w/ rejection during 6 months
- **Conversion Protocol**
  - Last dose of CNi was night dose
  - SRL started at 2mg daily the next day
  - No loading dose
  - SRL level adjusted on day 4, 7, 14
  - Goal: 5-15ng/mL

Watson, C.J. et al. Liver Transplantation 13:1694-1702, 2007




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**RCT of Late Conversion from CNi based to Sirolimus-Based Immunosuppression in Liver Transplant Recipients w/ Impaired Renal Function**

- **Results**
  - GFR statistically significantly better in SRL group at 3 months, but not at 12 months
  - No significant difference in mean changes in 24-hr urinary protein b/w groups
  - Acute rejection rate
    - 2 pts in SRL group (1 d/t low SRL 24-hr trough)
    - 0 pts in the CNi group

Watson, C.J. et al. Liver Transplantation 13:1694-1702, 2007




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**Abrupt Switch Method**

<ul style="list-style-type: none"> <li>• <b>PROS</b> <ul style="list-style-type: none"> <li>– Abrupt switch is simple to institute</li> <li>– Avoid overimmunosuppression</li> <li>– Avoids nephrotoxicity in the overlap period</li> <li>– No loading = less ADE's</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>CONS</b> <ul style="list-style-type: none"> <li>– Increased blood draws to ensure good 24-hr trough levels</li> <li>– ADE's associated with SRL</li> </ul> </li> </ul>
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Watson, C.J. et al. Liver Transplantation 13:1694-1702, 2007




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**Long-term Results in Renal Transplant Patients with Allograft Dysfunction After Switching from Calcineurin Inhibitor to Sirolimus**

- **Adult deceased donor kidney transplant**
  - **Included:** CNI-based regimen changing to SRL for chronic-allograft nephropathy (CAN)
  - 82% of pts had <150mg/day proteinuria, 13% had 150-500mg/day, 5% had 500mg-1gm/day proteinuria
- **Conversion Protocol**
  - SRL loading dose 12-15 mg, then 3-5 mg daily
  - CNI decreased 50% day 1, another 25% day 7, withdrawn day 14
  - Levels obtained weekly
  - SRL goal trough: 8- 12ng/mL

Bumbea V, et al. Nephrol Dial Transplant 2005; 20:2517-2523



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**Long-term Results in Renal Transplant Patients with Allograft Dysfunction After Switching from Calcineurin Inhibitor to Sirolimus**

- **Results**
  - Significant increase in renal function after the switch in 29 pts (67.4%)
  - 28% of pts developed overt proteinuria
  - 30.2% of pts withdrew due to ADE's



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**Different Switch Methods?**

- **Other protocols?**
- **Slow wean of CNI can be confusing to patients**
- **Some patients have a more difficult time remembering a once daily drug**
- **Compliance with blood draws and reliable timing of troughs**



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**PO → IV CNi Conversion**



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**PO → IV CNi Conversion**

- Many prescribers not familiar with conversion
  - May try to do a 1:1 conversion from PO to IV
  - Nephrotoxic/ ARF/ hypertension/ hyperkalemia
- Education to floor nurses about infusion rate/ time
- Be overly cautious in patients getting IV CNi



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**PO → IV CNi Conversion**

- Prograf
  - Vanderbilt: IV = 1/5 of the ORAL dose
    - EXAMPLE: 2mg q 12 hrs PO = 0.4mg IV q 12 hrs
  - 12 hour infusion per dose
    - 24 hour continuous infusion
  - Others?



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## PO → IV CNi Conversion

- Cyclosporine
  - **Vanderbilt:** IV = 1/3 of the ORAL dose
    - EXAMPLE: 150mg q 12hrs PO = 50mg IV q12hrs
  - 12 hour infusion
    - 24 hour continuous infusion
  - Others?



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## Conclusions

- Some data to support how to switch therapy
- Most centers create a protocol that the majority of team members are comfortable using
- May define pts as high and low risk
- Accurately measuring levels reduces risk to the patient
- There is more than one right way to do things



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## Bad Humor...



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