Pharmacology Switch Therapy: Evidence or Voodoo??

Jennifer N. Fosnot, PharmD
Vanderbilt University Medical Center
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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

Why would you switch a patient's immunosuppressant regimen?
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?

Potential Reasons for a Switch

- Tacrolimus
  - Headaches/ tremors
    - Regardless of trough level
  - Alopecia
  - Renal insufficiency/ CNI toxicity
  - BK virus/ other viruses?
  - Cancer
  - Post-Tx Diabetes Mellitus
  - General “intolerance”

- Cyclosporine
  - Rejection
  - Gingival Hyperplasia
  - Hirsutism
  - Renal Insufficiency/ CNI toxicity
  - Cancer
  - Hypertension
  - General “Intolerance”

Potential Reasons for a Switch

- Sirolimus (Rapamune)
  - Peripheral edema
  - Diarrhea
  - Proteinuria
  - Pulmonary fibrosis/ other issues
  - Upcoming surgery
  - Unexpected surgery
  - General “Intolerance”
  - Insurance issues?
Potential Reasons for a Switch

Cellcept (MMF) or Myfortic (MPA)

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

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

Or is it all Voodoo??

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”
Recommendations

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

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
Cellcept → Myfortic Switch

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

Sirolimus → CNi Switch Method
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

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
**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

- **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

- **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
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


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


Abrupt Switch Method

- PROS
  - Abrupt switch is simple to institute
  - Avoid overimmunosuppression
  - Avoids nephrotoxicity in the overlap period
  - No loading = less ADE’s

- CONS
  - Increased blood draws to ensure good 24-hr trough levels
  - ADE’s associated with SRL

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


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

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
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

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?
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?

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

Bad Humor...
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