MTOR-Inhibitors – switch from CNI

Introduction

Commercially available drugs

- sirolimus

- everolimus

Mechanism of action. Bind to FK binding protein and modulate the activity of mTOR, in turn inhibits IL2-mediated signal transduction and results in cell-cycle arrest. Act on T and B lymphocytes to prevent cell proliferation.

Pharmacokinetics

Absorption

- Peak concentration 1-2 hours
- Absorption altered by food
    - Sirolimus should be taken away from food
    - Everolimus should be taken consistently either with or without food

Metabolism and interactions

- Extensively metabolised in liver by CYP 3A4 (same as CNI) into inactive metabolites
- Potential interactions with some of the commonly used drugs in this population include
    - 3A inhibitors – increase drug concentration
        - Azoles
        - Non-dihydropyridine calcium channel blockers
        - Macrolide antibiotics
        - Lansoprazole and rabeprazole (but not pantoprazole or omeprazole)
        - Colchicine
        - Amiodarone
    - 3A inducers – decrease drug concentration
        - Rifampicin, isoniazid
        - Anticonvulsants
- Needs dose adjustments in hepatic impairment (but not renal impairment)
- Excreted in faeces, small percent in urine

Drug monitoring

- Long half-lives – sirolimus 60-72 hours, everolimus 24-30hours
- Measure trough after 5 days

Indications for Use

1. As alternative to CNIs

- Intolerant of CNI side-effects
- To be CNI free in an immunologically low-risk patient
- Consider in patients with chronic allograft injury and clear histological evidence of CNI toxicity
  BUT some evidence that stopping CNIs results in more de novo DSA
  - If eGFR >40ml/min/1.73m2 and urine PCR <50mg/mmol and 24hr proteinuria <500mg/day, CNI should be replaced with mTORi
  - If eGFR <40ml/min/1.73m2 or proteinuria >500mg/day, switch to mTORi not recommended

2. As alternative to antiproliferatives

- Intolerant of both MMF and azathioprine

3. Cancer

- Reduction in the incidence of skin cancers
- Kaposi's sarcoma

4. CMV/BK VAN

- Less CMV or BK when used to replace antimetabolite for primary immunosuppression

  (Cochrane review 2006)

Adverse Effects

1. Nephrotoxicity (not nephrotoxic alone, but combination with CNI cause synergistic nephrotoxicity)
2. Proteinuria
3. Pneumonitis – progressive interstitial pneumonitis observed in ~20% sirolimus use
4. Metabolic effects – dyslipidaemia, diabetes
5. Peripheral oedema
6. Mouth ulcers
7. Impaired wound healing
8. Infections
9. Myelosuppression (>CNI) including anaemia
10. Risk for AMR if CNI withdrawn

Avoid in patients with impaired glucose tolerance, dyslipidaemia, chronic wounds, or persistent proteinuria 500-1000mg/day.

Switching from CNI based maintenance immunosuppression

DOSING

No need to overlap with CNI

Sirolimus

- Early switch (<12 months) – start 5mg/day and check level 5-7 days later
- Aim sirolimus 6-8 ng/ml

- Later switch – start 3mg/day and check level 5-7 days later
- Aim sirolimus 3-5ng/ml

Everolimus

- Start 1mg /day and check level 5-7 days later
- Aim everolimus 4-9 ng/ml

NOTES

1. Halve the dose of Myfortic once level is consistently therapeutic
2. If indication is Chronic Allograft Dysfunction then maintain this lower dose of Myfortic
3. If indication is Cancer then slowly withdraw Myfortic (maintain Prednisolone) after 6 months