De Novo Concentration-Controlled Everolimus Is Associated with a Decreased Incidence of CMV Infection in Cardiac Transplant Recipients


Purpose

- CMV has an impact on progression of cardiac allograft vasculopathy (CAV).
- CMV+ recipients with CMV+ donors are at risk for developing CAV.
- The proliferation signal inhibitor (PSI) everolimus reduce the risk of CMV infection at 24 months compare to an azathioprine-based regimen.

Method and materials

- 6-month, multicenter, randomized, open label study
- Examined the safety, tolerability and efficacy of ST and RD CsA in addition to concentration-controlled everolimus and corticosteroids in de novo cardiac graft recipients.

Results

- 199 patients randomized to receive ST CsA (n=100) or RD CsA (n=99) from month 2 onwards.
- CMV infection:
  - positive antigenemia and/or PCR and/or seroconversion without signs and/or symptoms
  - 3.0% of the ST vs 7.1% of the RD
  - Laboratory evidence for CMV infection
    - 3% of ST and none of the RD group
  - CMV syndrome
    - 1% of ST patients and none of the RD patients
  - CMV tissue disease
    - 2% in ST and 1% in RD developing
Results

- Among high-risk patients (D+/R-), CMV infection occurred
  - 3/14 patients receiving prophylactic CMV treatment (6.3%) with a low incidence of CMV infection (6.3%) in high-risk patients receiving CMV prophylaxis.

Conclusions

- De novo immunosuppression with concentration-controlled everolimus + CsA in heart transplant recipients is associated with a low incidence of CMV infection.
- Also associated with a very low incidence of CMV infection (6.3%) in high-risk patients receiving CMV prophylaxis.

Impact of ACE-Inhibitor and Angiotensin Receptor Blocker Therapy on Development of Proteinuria after Switch to Sirolimus in Cardiac Transplant Recipients


Methods and Materials

- 61 long-term cardiac transplant patients switched from CNI-based to Srl.
- Divided into two groups: ACEi/ARB group vs. conventional antihypertensive therapy (CAT).
- Differences in development of PU and renal function were compared.

Purpose

- Switch to Srl due to renal impairment has been shown to be effective and safe after cardiac transplantation.
- However reports of increased incidence of proteinuria (PU) and a further decrease of renal function.
- To examine if ACEI/ARB therapy has an influence on development of PU after switch to Srl.

Results

- 55 patients (89%) received anti-hypertensive medication.
  - 7.25 (5.7) to 0.23 (0.13) (p=ns).
- Overall PU increased significantly from pre-switch 0.13 (0.02) to 0.23 (0.13) 24 months post switch (p=0.05).
- No difference between the two groups before switch:
  - ACEi/ARB: 0.19 (0.03)
  - CAT: 0.2 (0.05) (p=0.56)
- After 24 months: significant difference:
  - ACEi/ARB: 0.18 (0.03)
  - CAT: 0.42 (0.05) (p=0.05).
Results

- Creatinin clearance (CC) similar before the switch
  - ACEi/ARB: 48.8 ml/min (20.6-132.1)
  - CAT: 40.6 ml/min (17.3-120.2; p=ns.)
- After 24 months CC better in the ACEi/ARB group
  - ACEi/ARB: 58.8 ml/min (6.6-184.6)
  - CAT: 44.7 ml/min (10.8-84), p=0.05

Conclusions

- Development of proteinuria after switch to Srl can be significantly reduced with the use of ACEi/ARB therapy.
- Antihypertensive therapy of patients should be changed to ACEi/ARB before Srl is initiated.

Purpose

- Everolimus has been shown to slow progression of epicardial vasculopathy after heart transplantation (HTx).
- We studied its effects on the development of microvasculopathy after HTx.

Methods and Materials

- Prospective analysis of endomyocardial biopsies (Bx) from 84 patients (mean age 49 yrs, 73 men) four weeks (FU1=84) and one year (FU2=60) after HTx.
- Standard triple immunosuppressive therapy consisted of
  - Cyclosporine A
  - Everolimus or mycophenolate or azathioprine
  - Prednisolone.

In Bx (H&E):
- Stenotic microvasculopathy (ratio lumen to media 1) was classified
- Endomyocardial fibrosis and scars were evaluated by Sirius stainings (Zeiss Vision).
- Immunohistochemistry was done for smooth muscle cells using alpha-actin (Dako; clone 1A4).
- Graded according to a semi-quantitative scale (very strong positive=2, strong positive=1.5, positive=1, weak positive=0.5, negative=0).
### Results

- Everolimus applied to 27/84 (32%) patients in FU1 and 22/60 (37%) patients in FU2.
- Stenotic MVP present in 39/83 (47%) patients in FU1 and in 39/60 (65%) patients in FU2.
- In FU1, stenotic microvasculopathy lower treated with everolimus, but not significant (55% vs. 78%; p<0.07).
- Endomyocardial fibrosis in FU1 lower in everolimus (3.5±0.3 vs. 5.4±0.4%; p<0.002).

### Conclusions

- Everolimus might prevent the development of microvasculopathy after HTx by decreasing smooth muscle cell proliferation in small intramyocardial vessels.
- It seems to have positive effects on endomyocardial remodeling, i.e. to reduce the development of endomyocardial fibrosis and scars.

### Results

- Everolimus-treated patients have less amount of scars in FU2 (27.9±2.4 vs. 35.4±2.7%; p<0.041).
- Mean positive reaction for alpha-actin was less pronounced in patients treated with everolimus in FU2 (1.0±0.5 vs. 1.3±0.6; p<0.029).
- However, everolimus-treatment was not associated with incidence, prevalence or progression of microvasculopathy in H&E stainings.