Intra-patient variability of tacrolimus levels and cardiac allograft outcomes


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Introduction

- Intra-patient variability (IPV) of Tacrolimus (TAC) levels is a risk factor for poor long-term outcomes after renal transplantation. (Borra et al. Nephrol. Dial. Transplant. 2010)
- Erratic TAC exposure as assessed by the standard deviation of TAC levels has been shown to predict chronic lung allograft dysfunction and survival (Gallager et al. JHLT 2015)
- Measuring the intrapatient variability of immunosuppression drug levels is a tool that can be utilised to measure adherence.

Aim of the study

- To investigate whether high IPV of TAC levels within the first year after heart transplantation was associated with poor outcomes.

Methods

- Retrospective analysis of heart transplants from August 2007 - April 2015. Immunosuppression was induction with Rabbit Anti-Thymocyte Globulin, TAC, Mycophenolate and steroids. Steroids were weaned over 6-12 months and TAC dose was reduced, with target levels:
  - Months 1-3: 10-15ng/ml
  - Months 3-6: 8-11ng/ml
  - Months 6-12: 7-10ng/ml
  - Then reduced to 5-7ng/ml thereafter.
- Of the 147 transplanted, we excluded 65 patients who either died (n=32) or had TAC discontinued (n=34) within 1 year after transplantation.
- Coefficient of variance (COV) was defined as standard deviation / mean of TAC levels taken at monthly intervals for the 1st year after transplant. High variability (HV) was defined as a COV greater than the median.
- The proportion of time in therapeutic range was analysed
- Outcomes were treated Acute Rejection Episodes (ARE), Renal Impairment (RI) defined as eGFR <60 ml/min/1.73M², Cardiac Allograft Vasculopathy (CAV) detected by angiography or CT, Donor Specific Antibodies (DSA) and death. Also a composite end-point of medium-long-term outcomes.

Results

- The median COV of tacrolimus levels was 0.255
- Patients spent 55.9% of the time above the range and 11.2% below range (see fig) suggesting a bias in physician prescribing relative to the protocol. There was no significant difference between the 2 groups.
- There was no significant difference between the HV and non-HV groups in the incidence of poor outcomes (see table 2) but there was a strong trend towards a worse composite outcome.

Conclusions

While not statistically significant there was a trend towards more adverse events for patients with high TAC variability in the composite analysis.