Incidence of Coronary Artery Vasculopathy Has Decreased with Modern Immunosuppression: Insights from Clinical Trials in Organ Transplantation

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Introduction

Purpose: A non-randomized, prospective, multi-center, observational clinical trial in cardiac transplant (CT) recipients was conducted. We sought to determine alloimmune biomarkers associated with coronary artery vasculopathy (CAV) and the frequency of CAV. Intravascular ultrasound (IVUS) was utilized to analyze CAV at one month and one year after CT. In a 2003 report by Eisen HJ the incidence of CAV in CT pts immunosuppressed with steroids, azathioprine or everolimus, and cyclosporine ranged from 30% to >50%. (1) In this historical cohort of 634 pts ~50% received induction and the 1 year rate of moderate or >rejection ranged from 21.3 to 45.8%.

Aims

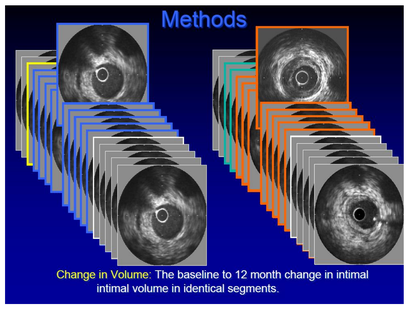
- To make serial IVUS measures in de novo heart transplant recipients.
- To compare conventional IVUS measures with volumetric measures
- To compare IVUS measures with biomarkers

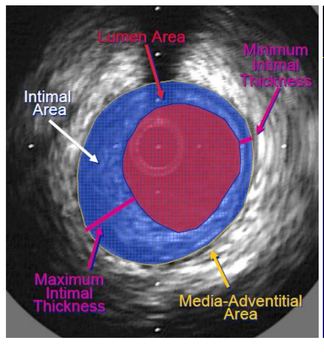
Methods

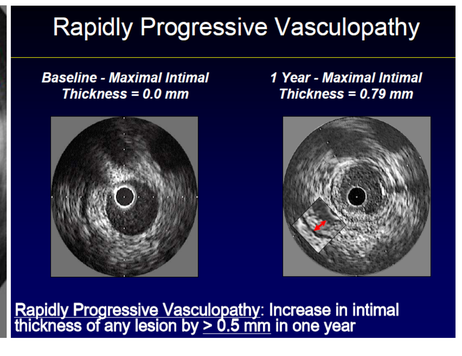
In the current study 54 CT pts were enrolled from 2007-2010 and followed for 1 year, mean age 52.5 (21-75) yrs, 20% female, 83.3% white. Induction received in > 52%. Tac/MMF maintenance in 75.9%, CSA/MMF 11.1. IVUS was performed at 12 centers at baseline and 1 year after CT, baseline mean 48.4 days, and follow up mean 370.2 days. Automatic pullback in the LAD using branch point landmarks; analyses performed by a core lab at Cleveland Clinic.

Methods (cont'd)

Rapidly progressive CAV defined as an increase in intimal thickness by >=0.5mm (any segment) in the first year was the IVUS primary endpoint. This endpoint has been associated with the composite endpoint of death, MI and angiographic CAV. (2)
Descriptive statistics were produced for the 54 subjects with paired IVUS data, including baseline, follow-up, and change in IVUS measures, as well as donor and recipient demographics and baseline characteristics. Pearson correlations were computed following log10 transformations to MIT, PAV, and TAV. All P-values were considered descriptive and exploratory, and P-values < 0.05 were considered noteworthy.







Results

54 patients had adequate baseline and 1 year IVUS exams with matched coronary segments suitable for exam and were analyzed by the core lab. Statin use in 72.2%, hypertension in 18.5%, diabetes in 27.8%, ischemic etiology 31.5%, mean donor age 31.2 years. BMI >30 in 20.4%. Rejection in year 1: 2R 7.4% n=4 3R 1.0% n=1

Results (cont'd)

MIT Mean Baseline mm	**0.39 ± (0.155)**
MIT Mean 1 Year mm	**0.45 ± (0.221)**
Change MIT mean mm	**0.06 ± (0.111)**
MIT ≥0.5 mm (% pts)	**20.4% (11/54)**
Total Atheroma Volume (TAV) baseline mm^3	**101.99 ± (40.16)**
Total Atheroma Volume (TAV) 1 Year mm^3	**115.85 ± (54.34)**
Change in normalized TAV	**13.86 ± (26.20)**
Percent Atheroma Volume (PAV) Baseline	**20.56 ± (4.75)** Q1 17.21 Q3 23.88
Percent Atheroma Volume 1 Year	**23.02 ± (6.77)** Q1 18.53 Q3 26.80
Change in PAV %	**2.46 ± (4.21)** Q1 0.44 Q3 3.40

Log10 Change MIT with Log10 Change PAV (r=0.897, p<0.001)
Log10 Change TAV with Log10 Change PAV (r=0.733, p<0.001)
Log10 Change MIT with Log10 Change TAV (r=0.879, p<0.001)

Subjects with a change in MIT >=0.5mm:
Log10 Change MIT with Log10 Change PAV (r=0.876, p<0.001)
Log10 Change TAV with Log10 Change PAV (r=0.620, p=0.042)

CAV with maximal intimal thickness (MIT) change >=0.5mm maximum 38% with class I or II antibodies compared to 33% without CAV; p value chi square 0.82.

Conclusions

- The incidence of rapidly progressive CAV has diminished over the past decade to ~20%.
- Conventional IVUS measures correlate with PAV which is a robust but currently unvalidated surrogate for CAV outcomes.
- Comprehensive biomarker analysis is ongoing but the current data do not support a causal relationship between alloantibodies and CAV.

References

1) Eisen, HJ, Tuzcu, EM, Dorent, R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003; 349:847.
2) Kobashigawa, JA, Tobis, JM, Starling, RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. J Am Coll Cardiol 2005; 45:1532.