Pathology Antibody-Mediated Rejection Plus Circulating Donor-Specific Antibodies Increase Development of Cardiac Allograft Vasculopathy After Heart Transplantation

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Abstract

Background: Several reports have correlated development of donor-specific antibody (DSA) to the development of cardiac allograft vasculopathy (CAV) after heart transplantation (HTx). Interestingly, patients (pts) who develop pathology antibody-mediated rejection (pAMR) by EMB do not always have detectable DSA at the time of the rejection episode. It is not known whether the combination of pAMR + DSA in the first-year after transplant leads to a greater incidence of subsequent CAV. We assessed the impact of first-year pAMR and DSA on the subsequent development of CAV by angiography at 3-years post-HTx.

Methods: Between 2010-2014 we assessed 400 HTx pts and divided them into those with first-year pAMR+DSA (n=31), pts with pAMR alone (n=53), pts with DSA alone (n=53) and pts who did not develop pAMR or DSA (n=263), We analyzed these groups for the development of 3-year CAV via angiography (per the ISHLT CAV grading scale). Additional endpoints included 3-year survival, and 3-year freedom from non-fatal major adverse cardiac events (NF-MACE: myocardial infarction, new congestive heart failure, percutaneous coronary intervention, implantable cardioverter defibrillator/pacemaker implant, and stroke).

Results: There was no difference in survival between the four groups. There was significantly less freedom from 3-year angiographic CAV noted in patients with pAMR+DSA (71.0% vs 92.2% vs 92.5% vs 87.1%, p=0.043, see table). Pts who had pAMR alone had similar outcomes in terms of angiographic CAV compared to pts without pAMR in the first-year post-transplant. Pts with DSA alone had similar outcomes compared to patients without DSA.

Conclusion: It appears that the combination of DSA and pAMR increases the risk of subsequent CAV development in heart transplant patients. Therefore, when detectable DSA is present in addition to pAMR, a heightened immune regimen (switch to a proliferation signal inhibitor) may be required.

Background

- Several reports have correlated development of donor-specific antibody (DSA) to the development of cardiac allograft vasculopathy (CAV) after heart transplantation (HTx).
- Interestingly, patients (pts) who develop pathology antibody-mediated rejection (pAMR) by EMB do not always have detectable DSA at the time of the rejection episode.
- It is not known whether the combination of pAMR + DSA in the first-year after transplant leads to a greater incidence of subsequent CAV.

Purpose

- To assess the impact of first-year pAMR and DSA on the subsequent development of CAV by angiography at 3-years post-HTx.

Methods

- Between 2010-2014 we assessed 400 HTx pts and divided them into those with first-year pAMR+DSA (n=31), pts with pAMR alone (n=53), pts with DSA alone (n=53) and pts who did not develop pAMR or DSA (n=263).
- We analyzed these groups for the development of 3-year CAV via angiography (per the ISHLT CAV grading scale).
- Additional endpoints included:
  - 3-year survival
  - 3-year freedom from non-fatal major adverse cardiac events (NF-MACE: myocardial infarction, new congestive heart failure, percutaneous coronary intervention, implantable cardioverter defibrillator/pacemaker implant, and stroke).

Demographics

Demographics	pAMR Alone (n=53)	DSA Alone (n=53)	pAMR + DSA (n=31)	No pAMR + No DSA (n=263)	P-Value
Mean Recipient Age, Years ± SD	56.8 ± 13.0	54.4 ± 10.5	52.1 ± 14.2	56.2 ± 13.5	0.311
Mean Donor Age, Years ± SD	34.8 ± 13.2	35.1 ± 13.4	33.1 ± 12.8	34.6 ± 13.2	0.915
Body Mass Index, Mean ± SD	25.6 ± 4.2	24.4 ± 4.7	25.4 ± 4.5	25.5 ± 4.5	0.475
Female (%)	26.4%	43.4%	51.6%	25.5%	0.003
Previous Pregnancy in Females (%)	71.4%	91.3%	93.8%	67.2%	0.034
Ischemic Time, Mean Mins ± SD	143.8 ± 53.6	165.9 ± 72.4	168.5 ± 59.2	161.0 ± 60.2	0.192
Primary Reason for Transplant, Underlying Diagnosis of Coronary Artery Disease (%)	39.6%	37.3%	30.0%	38.5%	0.897
Status 1 at Transplant (%)	83.0%	73.6%	83.9%	75.7%	0.471
Cytomegalovirus Mismatch (%)	23.1%	11.3%	23.3%	23.9%	0.248
Diabetes Mellitus (%)	24.5%	30.2%	32.3%	24.3%	0.671
Treated Hypertension (%)	43.8%	52.1%	53.8%	45.7%	0.719
Insertion of Mechanical Circulatory Support Device (%)	24.5%	28.3%	25.8%	23.6%	0.905
Prior Blood Transfusion (%)	61.4%	42.6%	62.5%	42.3%	0.042
Pre-Transplant PRA ≥ 10% (%)	26.4%	62.3%	74.2%	24.3%	<0.001
Pre-Transplant Creatinine, Mean ± SD	2.0 ± 1.7	1.3 ± 1.0	1.3 ± 0.5	1.4 ± 1.1	0.002
ATG Induction Therapy (%)	50.9%	60.4%	61.3%	33.5%	<0.001

Outcomes

Endpoints	pAMR Alone (n=53)	DSA Alone (n=53)	pAMR + DSA (n=31)	No pAMR + No DSA (n=263)	P-Value
3-Year Survival	84.6%	86.8%	87.1%	84.4%	0.903
3-Year Freedom from CAV	92.2%	92.5%	71.0%	87.1%	0.043
3-Year Freedom from NF-MACE	88.2%	88.7%	87.1%	89.0%	0.999

Results Summary

- There was no difference in survival between the four groups.
- There was significantly less freedom from 3-year angiographic CAV noted in patients with pAMR+DSA (p=0.043, see table).
- Pts who had pAMR alone had similar outcomes in terms of angiographic CAV compared to pts without pAMR in the first-year post-transplant.
- Pts with DSA alone had similar outcomes compared to patients without DSA.

Conclusion

- It appears that the combination of DSA and pAMR increases the risk of subsequent CAV development in heart transplant patients.
- Therefore, when detectable DSA is present in addition to pAMR, a heightened immune regimen (e.g. switch to a proliferation signal inhibitor) may be required.

Author Disclosures

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