Donor Specific Antibodies After Heart Transplantation: Can They be Treated?

Achilles Aiken, MD, Jignesh Patel, MD, PhD, Evan Kransdorf, MD, PhD, Adriana Shen, BS, Keith Nishihara, BS, Angela Velleca, BSN, RN, CCTC, Robert Cole, MD, Michele Hamilton, MD, Lawrence Czer, MD, Dominick Megna, MD, Xiaohai Zhang, PhD, and Jon A. Kobashigawa, MD

Cedars Sinai Smidt Heart Institute, Los Angeles, CA

Abstract

Background: The development of donor specific antibodies (DSA) after heart transplantation has been reported to occur in 12-13% of cases. These antibodies have been associated with increased development of cardiac allograft vasculopathy (CAV). DSA that have the ability to bind complement via the C1q assay (C1q+) have been reported to be more highly associated with the development of CAV. In our program, it is our policy to treat DSA with cardiac dysfunction and/or C1q+ DSA. It has not been established as to whether C1q+ DSA respond to desensitization therapy. Common desensitization therapies in our program for DSA include IVIG, rituximab, plasmapheresis, and bortezomib in various combinations.

Methods: Between 2010 and 2018, we assessed 43 heart transplantation patients who developed DSA and received desensitization therapy after heart transplant surgery. This group of patients included 25 patients with C1q+ DSA with the remaining 18 patients having cardiac dysfunction and DSA. Two of the C1q+ DSA patients also had cardiac dysfunction, which amounted to a total of 20 patient with cardiac dysfunction. All patients were treated with various combinations of IVIG and rituximab and/or plasmapheresis and bortezomib. Antibody binding of the immunodominant DSA (highest mean fluorescence intensity (MFI)) was assessed by Luminex neat assay for six months post-therapy. Regardless of C1q results, patients were also divided into DSA with cardiac dysfunction (left ventricular ejection fraction ≤ 40%) and DSA without cardiac dysfunction and assessed for the immunodominant antibody binding. DSA with cardiac dysfunction patients were also assessed for improvement of cardiac function following desensitization therapy.

Results: Patients with C1q+ DSA appear to have a similar response to desensitization therapy in terms of decreased immunodominant MFI after therapy compared to C1q- DSA. DSA with and without cardiac dysfunction also appear to have similar response to therapy. In patients with DSA with cardiac dysfunction, 75.0% (15/20 patients) had improved cardiac function following therapy.

Conclusion: A majority of heart transplant patients with DSA with and without C1q+ or with and without cardiac dysfunction did respond to desensitization therapy; however, it is not clear whether this treatment would lead to a decrease in cardiac allograft vasculopathy (CAV). Long-term follow up and a larger number of patients will be needed to answer this question.

Background

- The development of donor specific antibodies (DSA) after heart transplantation has been reported to occur in 12-13% of cases.
- These antibodies have been associated with increased development of cardiac allograft vasculopathy (CAV).
- DSA that have the ability to bind complement via the C1q assay (C1q+) have been reported to be more highly associated with the development of CAV.
- In our program, it is our policy to treat DSA with cardiac dysfunction and/or C1q+ DSA.
- It has not been established as to whether C1q+ DSA respond to desensitization therapy. Common desensitization therapies in our program for DSA include IVIG, rituximab, plasmapheresis, and bortezomib in various combinations.

Purpose

To assess whether donor specific antibodies (DSA), and C1q+ DSA specifically, respond to desensitization therapy.

Methods

- Between 2010 and 2018, we assessed 43 heart transplantation patients who developed DSA and received desensitization therapy after heart transplant surgery.
- This group of patients included 25 patients with C1q+ DSA with the remaining 18 patients having cardiac dysfunction and DSA. Two of the C1q+ DSA patients also had cardiac dysfunction, which amounted to a total of 20 patient with cardiac dysfunction.
- All patients were treated with various combinations of IVIG and rituximab and/or plasmapheresis and bortezomib.
- Antibody binding of the immunodominant DSA (highest mean fluorescence intensity (MFI)) was assessed by Luminex neat assay for six months post-therapy.
- Regardless of C1q results, patients were also divided into DSA with cardiac dysfunction (left ventricular ejection fraction ≤ 40%) and DSA without cardiac dysfunction and assessed for the immunodominant antibody binding.
- DSA with cardiac dysfunction was also assessed for improvement of cardiac function following desensitization therapy.

Demographics

Demographics	C1q + DSA (n=25)	C1q- DSA (n=18)	P-value
Mean Recipient Age, Years ± SD	50.4 ± 13.1	50.6 ± 16.5	0.966
Mean Donor Age, Years ± SD	33.1 ± 10.3	35.1 ± 15.4	0.617
BMI, Mean ± SD	24.9 ± 5.5	24.9 ± 4.7	0.982
Female (%)	24.0%	55.6%	0.055
Previous Pregnancy in Females (%)	83.3%	100%	0.375
Ischemic Time, Mean Mins ± SD	176.3 ± 51.6	168.8 ± 66.1	0.676
Primary Reason For Transplant, Underlying Diagnosis of CAD (%)	20.0%	27.8%	0.717
Status 1 at Transplant (%)	96.0%	77.8%	0.144
Cytomegalovirus Mismatch (%)	20.0%	16.7%	1.000
Diabetes Mellitus (%)	28.0%	38.9%	0.521
Treated Hypertension (%)	60.0%	50.0%	0.550
Insertion of Mechanical Circulatory Support Device (%)	28.0%	16.7%	0.480
Prior Blood Transfusion (%)	52.0%	33.3%	0.351
Pre-Transplant PRA ≥ 10% (%)	48.0%	44.4%	1.000
Pre-Transplant Creatinine, Mean ± SD	1.2 ± 0.4	1.3 ± 0.5	0.799
ATG Induction Therapy (%)	52.0%	72.2%	0.219

Outcomes

Endpoints	C1q+ DSA (n=25)	C1q- DSA (n=18)	P-value
Patients with Decreased Immunodominant MFI within 6-months post-therapy	60.0%	77.8%	0.325

Endpoints	DSA with Cardiac Dysfunction (n=20)	DSA without Cardiac Dysfunction (n=23)	P-value
Patients with Decreased Immunodominant MFI within 6-months post-therapy	65.0%	69.6%	1.000

Results Summary

- Patients with C1q+ DSA appear to have a similar response to desensitization therapy in terms of decreased immunodominant MFI after therapy compared to C1q- DSA.
- DSA with and without cardiac dysfunction also appear to have similar response to therapy.
- In patients with DSA with cardiac dysfunction, 75.0% (15/20 patients) had improved cardiac function following therapy.

Conclusion

- A majority of heart transplantation patients with DSA with and without C1q+ or with and without cardiac dysfunction did respond to desensitization therapy; however, it is not clear whether this treatment would lead to a decrease in cardiac allograft vasculopathy (CAV).
- Long-term follow up and a larger number of patients will be needed to answer this question.

Author Disclosures

J Patel has received research grants from Alexion Pharmaceuticals, Pfizer, Alnylam Pharmaceuticals and Astra Zeneca and is part of the advisory board/speaker bureau for Mallinckrodt Pharmaceuticals, Therakos and Akcea. J Kobashigawa has received research grants and/or honoraria from CareDx, Inc., Sanofi-Genzyme, CSL-Behringer and One Lambda Inc. and is part of the advisory board for Transmedics. L Czer has received research grants from St. Jude Medical and Abbott Laboratories. A Aiken, E Kransdorf, A Shen, K Nishihara, A Velleca, R Cole, M Hamilton, D Megna, and X Zhang have no financial relationships to disclose.