Factors Associated with Successful Downregulation of Anti-HLA Antibodies in Heart Transplant Candidates

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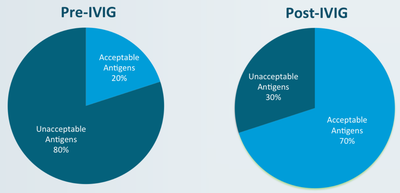
BACKGROUND

• A common barrier to transplant is sensitization to human leukocyte antigens (HLA)
- Occurs via pregnancy, blood transfusion, and transplants
- Significantly prolongs transplant wait-list times and mortality due to inability to receive an organ from a compatible donor

•To facilitate compatible transplantation, patients who are highly sensitized may be desensitized to:
- Increase donor pool
- Minimize wait list times
- Decrease post-transplant morbidity and mortality



•Intravenous immune globulin (IVIG) is commonly used to desensitize patients prior to transplant
- Mechanism: decrease IgG production
- Dosing: 2 mg/kg every 4 weeks
- Response is determined via panel reactive antibodies (PRAs) and median fluorescence intensity (MFI)
- Goal: deplete clinically important antibodies

•If IVIG is not successful, other therapies may be used to target other cellular mechanisms (bortezomib, carfilzomib, and rituximab)

OBJECTIVES

To determine the common factors associated with successful downregulation of anti-HLA antibodies in patients who are listed for a heart transplant.

Primary Endpoints
•Classify the response to IVIG therapy with regards to patient age, gender, class of antibodies, and history of pregnancy.

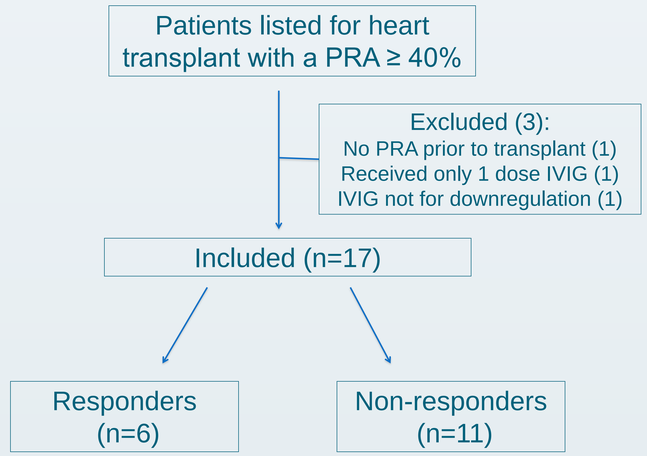
Secondary Endpoints
•Classify the response to IVIG therapy with regards to additional patient characteristics (VAD, blood transfusions, additional treatment, etc)

METHODS

•Retrospective, single-center study of highly sensitized patients (PRA ≥ 40%) listed for heart transplant

Inclusion Criteria
- Adult patients ages 18-89 year of age
- Candidates listed for heart transplant
- Received at least 2 doses of IVIG for downregulation of anti-HLA antibodies

Exclusion Criteria
- IVIG administration for reasons other than downregulation



RESULTS

Table 1: Patient Characteristics

Characteristic	Responders (n=6)	Non-Responders (n=11)	p-value
Age ± SD (years)	59 ± 6.4	53 ± 10.9	0.19
BMI ± SD (m^2)	27 ± 6.4	29 ± 4.9	0.52
Female, n (%) Previously pregnant, n (%)	2 (33 %) 2 (33%)	9 (82 %) 9 (82%)	0.11* 0.11
Black, n (%)	1 (16.7 %)	7 (64 %)	0.13*
Non-ischemic cardiomyopathy, n (%)	4 (67 %)	9 (82 %)	0.58
VAD, n (%)	6 (100 %)	10 (91 %)	1.0
Received ≥ 6 units blood, n (%)	3 (50 %)	4 (36 %)	0.59
*Trend towards significance			

Table 2: Treatment Characteristics

Characteristic	Responders (n=6)	Non-Responders (n=11)	P-Value
Doses of IVIG, median (IQR)	9.5 (7-18)	6 (2-10)	0.18*
Additional treatment, n (%)	2 (33 %)	5 (45.5%)	0.55
Pre-IVIG PRA, % (range)	88% (84-94)	83% (41-100)	0.42
Post-IVIG PRA, % (range)	11.8% (0-43)	79% (41-100)	**<0.001**
Class I antibodies prior to treatment, n (%)	3 (66.6%)	11 (100%)	0.11
Class II antibodies prior to treatment, n (%)	3 (33.3%)	6 (54.5%)	0.30
Started with both classes, n (%)	0 (0%)	6 (54.5%)	**0.04**
*Trend towards significance			

- Additionally, no patients had concomitant autoimmune diseases or previous transplants.

Table 3: Patient Outcomes

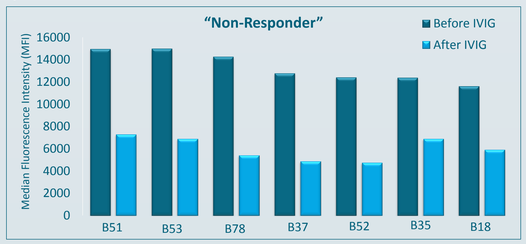
Gender	Race	PRA (antibody class present) Pre-IVIG	PRA (antibody class present) Post-IVIG	Doses of IVIG
Responders				
M	B	90 (I)	0 (0)	20
M	W	84 (II)	0 (0)	6
M	W	87 (II)	0 (0)	11
M	W	90 (I)	28 (I)	25*
F	W	88 (I)	0 (0)	8*
F	W	94 (I)	43 (I)	6
Non-responders				
F	B	98 (I)	94 (I)	2
F	B	95 (I)	88 (I)	4*
F	B	100 (I & II)	100 (I & II)	11
F	B	95 (I & II)	90 (I & II)	19*
F	B	76(I & II)	48 (I & II)	19
F	B	100 (I & II)	99 (I & II)	8*
F	W	72 (I)	72 (I)	2
F	W	99(I & II)	99 (I & II)	9
F	W	95 (I)	96 (I & II)	6*
M	B	41 (I)	41 (I)	2*
M	W	42 (I)	42 (I)	2
Gender (M: Male, F: Female), Race (B: black, W: white); *Additional Treatment				

CONCLUSIONS

- IVIG can be an effective means of downregulation for some patients
- IVIG may be more effective for
  - Caucasian
  - Males
  - Longer durations of treatment
  - Eliminating one class of antibodies versus two classes

Limitations
- Retrospective design
- Small sample size
- Number of IVIG doses varied between patients
- Unable to discern the effects of pregnancy on response to treatment
- Concomitant treatment with other agents for downregulation

Future Directions
- Redefine response to IVIG based on median fluorescence intensity (MFI)



REFERENCES

1. Castleberry et al. Circulation 2014; 129: 2313-2319

DISCLOSURE

None of the aforementioned authors on this project have any financial or personal relationships with commercial entities that may have directly or indirectly conflicted with subject matter of this research.