Post-Heart Transplant Conundrum: Do All Post HTx DSA Require Treatment? What About HLA Abs
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To Treat or Not Treat DSA
Objectives
• What is the impact of pre-formed and de-novo DSA on heart transplant (HTx) outcomes?
• Are all DSAs equally deleterious to the allograft?
• Is treatment warranted for all DSAs?

I have financial relationship(s) with:
CSLBehring – Research Grant

AND
My presentation does include discussion of off-label or investigational use.
Bortezomib
HLA antibodies may appear before loss of allograft function and are highly predictive of poor outcome

Questions to be answered:
1) Are antibodies detected solely by high-sensitive techniques clinically relevant?
2) How often to monitor for DSA post-transplant?
   Consider risk stratification

The impact of donor-specific HLA antibody (DSA) pre-formed and de-novo in adult and pediatric HTx (2010-2016) has been shown on:
1) Graft Survival (GS)
2) Development of Antibody Mediated Rejection (AMR)
3) Development of Cardiac Allograft Vasculopathy (CAV)

Summary:
1) Allosensitization depicted by PRA > 10% is associated with poor outcome in both cohorts.
2) Similar risk factors identified in both cohorts for the development of de-novo DSA.
3) The frequency of assessment of DSA post-transplant and the phenotype of DSA memory vs. true de-novo is being addressed by ongoing multicenter studies.

Multivariable analysis indicated de-novo persistent DSA to be an independent predictor of poor patient survival (p=0.0001 HR=4.351) along with DR mismatch and patient age.
Persistent Class II majority DQ specific DSA worst outcome.

Survival by DSA Group

TRANSIENT DSA
LOW RISK
NO TREATMENT

Sub-clinical
Pre-clinical

Early DSA Detection
Based on risk assessment of HTx candidate

Circulation 2015

Determinants and Outcomes of Accelerated Arteriosclerosis
Major Impact of Circulating Antibodies

Alexandre Leudy,* Dové Vugia*-Bar, Denis Vugia*, Olivier Asvelt,
Jean-Paul Durivau-Baynon, Jean-Philippe Emmerza, Patrick Benest, Denis Grole,
Christophe Lagendorf, Xavier Janss,† Carles Lluchar§

Circulating donor-specific anti-HLA antibodies were significantly associated with occurrence of major adverse cardiovascular events. The study was an independent, traditional risk factors. [Circ Res 2013;112:492-502. DOI: 10.1161/CIRCRESAHA.112.305042]
Presence of DSA and C4d Deposition at any strength is associated with increased risk CAV.

Interpretation of DSA based on SAB for guiding patient management and treatment.

Are all DSA clinically relevant?
SURROGATE CROSSMATCH

A physical crossmatch with a “surrogate” donor to determine the presence of an HLA antibody or to determine the strength of an HLA antibody....

DISCONNECT SAB MFI/Functional Reactivity of HLA-Ag

Aspects to consider: FALSE POSITIVE BEADS (DENATURED EPITOPES?)

Use Flow Cytometry Crossmatch to demonstrate false reactivity in SAB

NO RISK FOR AMR
NO TREATMENT of DSA to B37

SURROGATE CROSSMATCH

Pediatric Heart Candidate with pre-formed DSA

5327 MFI
SURROGATE CROSSMATCH

- FLOW CYTOMETRY XM w/SURROGATE DONOR NEGATIVE
- B8 REMOVED AS UNACCEPTABLE
- PATIENT TRANSPLANTED WITH B8 DONOR

DAY ±147, anti-B8 STILL PRESENT BUT NO GRAFT DYSFUNCTION!!!
NO TREATMENT Pre or Post- HTx

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When should DSA be treated?

- Strength of DSA on SAB (MFI)
- Titer of DSA
  - (Dilution of sera and test SAB)
- Persistent vs Transient DSA
- Complement Binding DSA
  - Presence or Absence of Complement Fixing (CF IgG1/IgG3): Isotype in the Mixture
  - Relative level of CF vs. non CF Isotype in the Mixture
  - Titer of HLA-specific IgG (1:32 to 1:64)

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When to Treat

Characteristics of DSA

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- Titer of DSA
- Persistent vs Transient DSA
- Complement Binding DSA
  - Presence or Absence of Complement Fixing (CF IgG1/IgG3): Isotype in the Mixture
  - Relative level of CF vs. non CF Isotype in the Mixture
  - Titer of HLA-specific IgG (1:32 to 1:64)
Increased level of DSA HLA-B7 early post-HTx (memory) and complement binding reactivity correlated with AMR. 

Persistent AMR requires prolonged treatment.

Increased Immunosuppression in HTx Day 6 in response to increased level DR4 DSA (MFI) and C1q reactivity in absence of graft dysfunction.

The utility of DSA surveillance in identifying risk of pAMR:
- Increased in strength of DSA correlated with pAMR severity.
Question with Audience Participation
Case of Early Memory Response

1. Historical (1 year pre-Tx) Positive Class II DSA (>4000 MFI), at the time of HTx low level (<2000 MFI), B cell VCXM for CDC/FC/PC Negative
   1. Consider HTx : YES or NO
   2. Yes with appropriate plan for antibody removal therapy
2. Following HTx how soon and how often monitor DSA?
   1. Begin DSA monitoring post-HTx: week 1, 1 month, 3 month
   2. High risk for AMR, monitor first week for memory response and if treated, pre- and post-treatment
3. Determine efficacy of treatment by measuring the impact on DSA level
   1. Test by SAB only for change in MFI or test for change in DSA titer by dilution
   2. Change in DSA titer pre- vs. post-treatment

Differences in DSA titer AMR

Memory Response Associated with Early AMR in HTx

Response to therapy:
- High titer DSA DR13 persisted longer
- Low titer DSAs DP3 and DR52
- DSA DR13: on day 7 and 31 had similar SAB MFI >10,000 but the titer was 50 fold lower on day 31 (post therapy) vs. day 7 (diagnosis of AMR)
Increase in titer of DSA prior to diagnosis of Graft Dysfunction Day 13

Case of De Novo DSA associated with non-compliance 5y post-HTx
1) Multiple Class II DSA (DQ6, DR51, DR53, DR7 >6000 MFI)
2) Strong C1q binding

Post PLEX and IVIG Treatment:
1) Class II DSA drop <3000 MFI
2) All DSAs C1q negative
3) 2 years post treatment DSA negative

ATC 2016

Pediatric Heart Transplantation Across a Positive Crossmatch is Associated with High Rates of AMR but No Differences in Short-Term Graft Loss, Graft Dysfunction and Death (CTOTC-04)

Steven A. Webber, Vanderbilt University School of Medicine
Do All Post-Heart Transplant DSA Require Treatment?

- No!
- Intervention should be considered:
  - Correlation of presence of DSA with biopsy histology and/or clinical dysfunction.
  - High risk patient (previously sensitized, non-adherent) with persistent DSA (titer, complement fixing ability).
- Ongoing and future CTOT studies in adult and pediatric HTx should provide clinically relevant information regarding DSA treatment.

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References