Donor Specific Antibodies - Different (Immunosuppressive) Strokes for Different Folks

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University of Texas Health Science Center
CEOT 2019
Disclosures

• Will mention the off label therapy directed at DSA
**Mrs. K. 56 yo**

5 mo post transplant for IPF

- PFTs: Progressively improving since transplantation
- Clinical: stable, active
- Pneumonia at 3 mo Resolved.

**ACR:** A2B0 at 3 months. Resolved at next biopsy.

**AMR:** Path and C4d Negative

**DSA:** No pre-formed DSA. De Novo DSA at 3 month: DQ5 2900 MFI, DQ 6 4200

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**Mrs. E. 60 yo**

5 mo post transplant for IPF

- PFTs: 18% decline FEV1 last month
- Clinical: Worsening exercise tolerance
- No infection

**ACR:** Negative for 4 months.

**AMR:** Negative C4d. Mild chronic interstitial thickening.

**DSA:** No pre-formed DSA. De Novo DSA at 3 month: DQ5 2400 MFI, DQ 6 3200
What therapeutic options do we have for these two patients?
If the two therapeutic decisions are different, what were those decisions based on.
“HLA antibodies and Lung Transplantation”: Publications by year
These studies provide evidence establishing a relationship between DSA and outcomes post transplantation.

Hachem, AJT 2018; 18: 2285
Hachem JHLT 2010; 29: 973
Safavi JHLT 2014;33:1273–1281

Tinkanen AJRCCM  2016 194L 5
Lobo 2013 JHLT 32: 70

Morrel JHLT, 33, No 12, December 2014

Barhat Ann Thorac Surg 2010
Monica

On Marshall hgb stable 9.6

ok

Delivered

Today 06:59

I am seeing mrs k and Mrs e right now
What are your recommendations for their DSAs?
These studies provide evidence establishing a relationship between DSA and outcomes post transplantation.

Do these answer the daily clinical questions that arise regarding DSA in our individual patients? (ie: Mrs. K and Mrs. E are waiting for an answer.)
I am seeing Mrs K and Mrs E right now. What are your recommendations for their DSAs?

🤔 uhm—if you can wait 20 minutes—I will have ALL the right answers.
In 20 minutes, you will not have all the right answers for when to use which of these therapies for DSA and on whom...

- PP
- Carfilzomib
- Observation
- Need more data
- IVIG
- Steroids
- Eculizumab
- Rituximab
- Bortezomib
Or what to definitively use for each DSA scenario you come across...

- DSA is Class I versus Class II?
- DSA is De Novo?
- DSA is persistent
- DSA appears early
- DSA is complement binding
- There is a high titer?
- There are no other AMR characteristics present
- DSA appears early
“Match the correct therapy to each patient”.

- Mrs. E: DSA is persistent
  - Plasmaphoresis
- Mrs. K: DSA appears early
  - Carfilzomib
- DSA is Class I versus Class II?
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“Match the correct therapy to each patient”.

Mrs. E
- DSA is Class I versus Class II?
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Mrs. K
- DSA is persistent
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Rituximab
- Bortezomib
- Carfilzomib

Plasmaphoresis
- Eculizumab

IVIG
- Steroids

DSA is complement binding
These results show us that DSA’s can lead to graft dysfunction, AMR, CLAD and decreased survival... but what they don’t show...
… is which patient with a specific DSA will benefit from a particular therapy

One-size fits all

Personalized therapies tailored to individual characteristics
DSA associated with a wide spectrum of effects on allograft.

Absence of injury

Acute AMR

Indolent changes leading to CLAD

Not all DSA’s carry the same risk for these outcomes.
What characteristics of DSA’s should we look for when evaluating for treatment? Do these studies provide this?

- Preformed/De Novo
- Complement binding
- Persistent/recurring
- MFI/Titers
- IgG subclass
- Dilution
- HLA/non-HLA
2016 ISHLT consensus focuses on DSA as an integral characteristic when defining AMR...

Measurable graft dysfunction

AMR

- Clinical
- Subclinical

No graft dysfunction

Degree of Certainty

- AMR
  - Clinical
    - Possible
    - Probable
    - Definite
  - Subclinical
    - Possible
    - Probable
    - Definite
Each DSA is unique, each patient is unique, each situation is unique.

- Complement binding
- Preformed/De Novo
- Histology/C4d
- MFI/Titers
- IgG subclass
- Clinical Status
- Dilution
Do we have the tools we need to identify individual patients with DSA who may be at higher risk for AMR, CLAD and decreased survival?
What we use now: Useful clinical tools

Patient

HLA lab

Pathology

Pulmonary function
All of these diagnostic tools have inherent issues

- Low sensitivity
- Low specificity
- Sampling error
- Poor reproducibility
- Inter-observer variability
- Experience dependent
- No definite thresholds
- Variability
- Low prognostic capacity
- Other etiologic factors
- False positive
- False negative
- Discordant results
- Specificity
Sometimes, elements of the work up is missing.
Sometimes, only the DSA is positive.

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<th>Histology</th>
<th>C4D</th>
<th>DSA</th>
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<tr>
<td>Definite</td>
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### Challenges in DSA lab assessment

<table>
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<th>Challenges</th>
<th>Interpretations</th>
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<tr>
<td>False positive result</td>
<td>Clinically irrelevant HLA-ab to denatured antigens</td>
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<td>Nonspecific binding of IgG (ie: following therapy with IVIg)</td>
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<td>False low MFI or negative results</td>
<td>Inhibition of SAB assay due to intrinsic and extrinsic factors</td>
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<td>Lack of donor antigen in the Luminex bead assay</td>
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<td>Discordant results between SAB-MFI and reactivity using cellular targets</td>
<td>False low MFI: DSA to a shared target present on multiple beads</td>
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<td>Assessment of DSA specificity</td>
<td>Incorrect assignment when donor allele is missing</td>
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<td>AMR features without serum HLA DSA</td>
<td>Presence of non-IgG DSA of non-HLA Ab of DSA against a non-typed HLA gene or DSA against an HLA allele not represented in the SAB assay</td>
</tr>
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</table>
Limitations of our current knowledge may lead to opportunity...

- Reflect the need for additional diagnostics then is provided by our conventional histologic, serologic and functional work up. (ie: be addressed by newer techniques)

- Reflect the need for better use of our current techniques (ie: closer and more standardized monitoring, increasing the sensitivity and specificity of our present analyses).

- May be a combination of both.... (ie: molecular profiling added to new histologic findings or cfDNA added during close monitoring of pulmonary function).
Tools we use now
How we use them
May not be enough to guide individualized therapy

HLA lab
“eplet Matching”

Pathology
“alveolar septal widening”

Pulmonary function

Patient
“personalized” analyses

Understand Mechanisms
- Immune Risk Stratification

Biomarker Discovery
- Early Diagnosis
- Monitoring Graft Function
- Treatment Response

Therapeutic Discovery
- Novel Targets
- Drug Repurposing

Computational analysis

Nanotechnology
Epigenetic
Cell free DNA
Genomics
Microarray
Metabolomics
Microbiome
DNA/RNA sequencing
Molecular microscope
Proteomics
Immune Repertoire

Transplantation 2017: 101: 8
Maybe with these combinations we could *objectively* and *confidently* assess the risks of each patient with DSA.

Treat those who would benefit from therapy and hold on therapy on those who would not.
How do we get there?

Data, lots of data

Implementation of a large-scale diagnostic registry is crucial to identify and develop risk characteristics and eventually lead to successful precision therapy.
1. Data collection

- Current and novel data points.

- Amalgamation of clinical, historical, behavioral, functional and genetic data important in risk stratification.

- Prospective data collection with *serial* measurements.
What’s the natural history of a particular DSA?

+de novo DSA
Centralized multi-center registry

- Agree on a standardized diagnostic schedule for monitoring:
  - Frequency
  - Types of tests
  - Patients to test
  - Cost-benefit
  - Outcomes required to follow
- Determine the outcomes in a consistent manner
- Define DSA attributes that correlate with risk
- Consider therapeutic options and post therapy follow up
2. Risk Assessment is a continuous endeavor.
3. Individualized “precision” therapy: Not just how to treat but who to treat and when?

• **Who do we treat?**
  • Specific patients?
  • Specific antibodies?
  • Specific titers?

• **When do we treat?**
  – Asymptomatic or wait for symptoms?

• **How do we treat?**
  – Do we treat all antibodies the same?
  – How many courses/cycles of treatment is appropriate
What outcomes do we expect after “Successful treatment” of De Novo DSA?

• Antibody clearance (what is the definition?)*
• Antibody reduction (what constitutes success?)
  – Reduction of what? (MFI? Titer?)
  – How much of a reduction is necessary?
• Prevention of graft dysfunction?
• Prevention of AMR, CLAD?
• Survival?
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Hippocrates

“It is far more important to know what sort of person the disease has, than what sort of disease the person has.”
Thank you!
Any questions?

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