Is it safe to transplant against HLA DSA in cardiothoracic patients? – development and implementation of national Guidelines

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Introduction

- Overview of cardiothoracic transplant activity
- Is HLA important?
- Challenges
- Avoid, ignore or remove HLA DSA?
- Development of Guidelines for transplanting against DSA in the UK
- The Newcastle experience
Indications for cardiothoracic transplantation

Heart

• Adults - idiopathic dilated cardiomyopathy, ischaemic cardiomyopathy. Less commonly – congenital heart disease, valvular heart disease, infiltrative conditions (e.g. sarcoid, myeloid)

• Paediatric – dilated cardiomyopathy, congenital heart disease
Indications for cardiothoracic transplantation

Lung

• Advanced COPD, idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to α1-antitrypsin deficiency, idiopathic pulmonary hypertension
<table>
<thead>
<tr>
<th>ORGAN</th>
<th>Transplants Reported from July 1, 2012, through June 30, 2013</th>
<th>Total Transplants Reported through June 30, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>3,809</td>
<td>116,104</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>66</td>
<td>4,488</td>
</tr>
<tr>
<td>Lung</td>
<td>3,550</td>
<td>49,642</td>
</tr>
</tbody>
</table>
Adult and Pediatric Heart Transplants
Number of Transplants by Year and Location

NOTE: This figure includes only the heart transplants that are reported to the ISHLT Transplant Registry. As such, the presented data may not mirror the changes in the number of heart transplants performed worldwide.
Adult and Pediatric Lung Transplants
Number of Transplants by Year and Procedure Type

NOTE: This figure includes only the lung transplants that are reported to the ISHLT Transplant Registry. As such, this should not be construed as representing changes in the number of lung transplants performed worldwide.
Deceased donor heart programme in the UK, 1 April 2004 - 31 March 2014, Number of donors, transplants and patients on the active transplant list at 31 March

Source: Transplant activity in the UK, 2013-2014, NHS Blood and Transplant
Deceased donor lung and heart/lung programme in the UK, 1 April 2004 - 31 March 2014, Number of donors, transplants and patients on the active transplant list at 31 March

Source: Transplant activity in the UK, 2013-2014, NHS Blood and Transplant
Clinical significance of HLA antibodies in Cardiothoracic transplantation

- Early studies based on CDC showed that pre-transplant donor-specific HLA antibodies are associated with hyperacute or accelerated rejection of thoracic organ allografts - Singh G et al, Clin Immunol Immunopathol 1983; Smith JD et al, Transpl Immunol 1993; Itescu et al, Circulation 1998

- More recent studies have shown that donor specific HLA antibodies detected by Luminex assays are also associated with increased graft loss and increased acute rejection in cardiac recipients – Stastny P et al, Transplantation 2007; Smith JD et al, Am J Transplant 2007; Mahle WT et al, j Heart Lung Transpl 2011
Clinical significance of Crossmatching in CT transplantation

- Early studies – a positive CDC IgG T cell crossmatch is associated with accelerated graft failure for heart and heart/lung transplants – Smith JD et al, Transplant Immunol 1993

- Flow cytometric crossmatching has shown a correlation with increased early acute rejection episodes in heart transplantation and severe graft dysfunction in lung transplant recipients – Przybylowsk iP et al, Transplantation 1999; Scornik JC et al, Transplantation 1999
Cardiothoracic transplantation

- Life expectancy is often very limited without a transplant and quality of life very poor
- Replacement therapy is usually short term only
- Unlike renal transplantation, acceptable ischaemia time is short (4 hr for hearts, 6-8 hr for lungs)
- Prospective crossmatching is logistically difficult, and limits donor pool
- Listing a patient for a prospective crossmatch often means patients succumb to end stage disease while on waiting list
- Pre-transplant crossmatching is performed via a vXM in most instances
- In the UK, cardiothoracic organs are not allocated based on HLA matching
HLA antibody detection

- Luminex-based SAB assays have made virtual crossmatching very safe
- Increasing numbers of patients are reported as sensitised in the Luminex era, decreasing chances for transplantation
- Avoid, ignore or remove antibodies?
Consequences of avoiding HLA DSA

Antibody Effects

Latest Cytotoxic Antibodies (%)
Orthotopic Heart Transplants 1990-2013

Latest Cytotoxic Antibodies (%)
Orthotopic Heart Transplants 2000-2013
Clinical Implications

• Treating all antibodies detected by Luminex SAB as ‘unacceptable antigens’ for transplant may have serious consequences for individual sensitised cardiothoracic patients

• Considerable efforts in many laboratories for better definition of clinically significant antibodies

• Need for improved tools for immunological risk stratification

• Need to balance individual patient needs v optimal organ usage

• Early experience of transplanting against HLA antibodies, including antibody removal
Early Newcastle experience - adults

- Four patients (pre-2012)
- All multiparous women
- All in cardiac failure in their 20/30s
- All with limited life expectancy
- All screened by Luminex SAB
Early Newcastle experience - adults

- In end stage organ failure, multiple HLA antibodies present.
- High titre antibodies present when heart available (20000 MFI Luminex) CDC +++

Case 1
- Transplanted (222 mm) and treated aggressively
- 6 months of poor organ function
- Antibodies controlled after 1 month
Early Newcastle experience - adults

Case 2
- Transplanted (001 mm) and treated aggressively
- Negative prospective XM missed antibodies. Good function to date

Case 3 and 4
- Remove antibodies with Therasorb columns
- Transplant when negative
- Case 3 transplanted alive 5 years post transplant
- Case 4 died waiting whilst negative for HLA
A US perspective

- Patients with multiple HLA antibodies transplanted (n= 8) and results compared with patients with low sensitisation levels (n=23)
- Transplanted without prospective XM
- Triple volume intra-operative plasma exchange followed by Alemtuzumab (Campath) induction for sensitised patients (basiliximab for low PRA patients)
- 7/8 sensitised patients have positive retrospective CDC XM
- No difference in one year survival between groups
- Significant difference in AMR in first year (38% vs 4%) and a higher risk of cellular rejection beyond one year
- Pheresis allows a short window free of HAR, during which patients can be induced with alemtuzumab

– Lick SD et al, Ann Thoracic Surg 2011
Early Newcastle experience - paediatric

- 11 HLAai Transplants 2009-2012
- Serial testing prior to transplant
- All received blood volume exchange pre-implantation
- Desensitisation was performed dependent upon sensitisation levels and ABO incompatibility
- 3 were CDC positive at time of transplant
- 7 received ATG induction, 4 had Basiliximab
- Outcomes comparable to non-sensitised recipients
Early Newcastle experience - paediatric

- Median age 1.3 (0.5-12) years
- 6 ABOi + HLA ai
- 4 underwent pre-transplant desensitisation
- Post transplant 6 received PEx or IA
- Rejection - 5 had none, 5 had one mild episode and 1 had severe
- 10 are alive 1.5 – 4 years post-transplant
The next step

• Can Guidelines for HLAi cardiothoracic transplantation be developed by a national partnership between H&I laboratories and cardiothoracic transplant units?
  – Development of NHSBT-ODT Cardiothoracic Advisory Group Guidelines (CTAG) for sensitised patients
What do the EFI Standards say?  
(Section H) v 6.2

- In cases where patients are at a high risk for allograft rejection ..., donors and recipients must be typed for HLA-A, B and DR antigens

- Cardiothoracic patients must be screened for the presence of HLA alloantibodies, unacceptable specificities must be defined or a prospective crossmatch must be performed

- Sera from patients at a high risk for allograft rejection should be prospectively crossmatched

- Wherever possible, non-renal organs for recipients at high risk for allograft rejection should come from crossmatch negative donors as defined by the laboratory and transplant programme
Cardiothoracic Transplant Centres in the UK

- Glasgow
- Newcastle (incl Paediatric)
- Manchester
- Birmingham
- Papworth
- Harefield
- GOS (Paediatric)
NHSBT-ODT Cardiothoracic Advisory Group (CTAG) Guidelines

• Data analysed from all H&I laboratories supporting cardiothoracic transplantation. Specificities reported and MFI values for EQA samples compared

• Antibodies considered to be due to non-allogeneic stimulation (e.g. infection) or characteristic of a known false positive reaction pattern can be excluded from being reported

• All remaining antibody specificities must be reported, above laboratory MFI cut off for positivity

• Each positive HLA specificity should be assigned a risk based on its MFI level.

• Treat all specificities for all HLA antigens equally

• Treat heart and lung patients according to the same criteria. Also Adult and Paediatric patients
CTAG Guidelines

• Risk Level 1 – HLA specific antibodies not detectable

• Risk Level 2 – HLA specific antibodies with cumulative MFI <2,000. Minimum risk of hyperacute rejection but greater than standard risk of rejection

• Risk Level 3 - MFI 2,000 - 5,000. Low risk of hyperacute rejection but significant risk of early rejection and antibody mediated graft damage. Immediate pre-transplant antibody reduction advised when feasible

• Risk level 4 - MFI > 5,000. Transplant veto apart from exceptional cases. Further testing such as CDC tests, or complement fixation in Luminex assays (C1q, C3d or C4d) should be considered in these cases to further refine risk profiles
CTAG Guidelines

- Prior to transplant listing, patients should be screened for HLA specific antibodies on at least 2 independent samples (wherever possible), with at least one test employing a solid phase assay.

- Sensitised patients should be screened every 3 months, with 6 monthly testing of unsensitised patients. Samples should also be tested after known sensitising events.

- For unsensitised patients and patients with clearly defined sensitisation, a pre-transplant vXM should be performed. A wet XM should be performed retrospectively.

- If patient is very highly sensitised, a prospective XM may be required.

- Post-transplant antibody monitoring should be performed according to an agreed schedule.
CTAG Guidelines

- Guidelines now incorporated into revised British Society for Histocompatibility and Immunogenetics/British Transplantation Society Guidelines for the detection and characterisation of clinically relevant antibodies in allotransplantation (2014)

www.bshi.org.uk and www.bts.org.uk
Newcastle Protocol

• Devised in conjunction with H&I and the clinical team

• All patients tested with Luminex Identification beads to negate SAB problems such as bead saturation/complement

• 2nd test Luminex SAB for stratification

• Samples tested three monthly

• Current sample result used as definitive

• Historic specificities counted as low additional risk but noted
Newcastle Protocol

- Each HLA specific antibody listed by strength
  - MFI < 500 negative
  - MFI 501 - 1200 Low
  - MFI 1201 – 2000 Medium
  - MFI ≥ 2001 – High
- Transplant OK with ≤ 2 individual ‘Low’ or 1 ‘Medium’ MFI specificities. Transplant against High MFI specificities in extremis only
- Assess DQA and DP antibodies as potential ‘hits’ if donor DQA/DP type not known
- Clinical protocol agreed
The Newcastle experience

- Local protocol agreed and adopted in April 2012
- 54 transplants – 28 hearts 26 lungs
- 17 historic specificities – negative in at transplant sample
- 22 low MFI (4 with 2 specificities)
- 9 medium MFI
- 6 high MFI (3 children, 1 in extremis, 1 new at transplant, 1 previous low)
- All CDC XM negative, 4 FXM positive
Post-transplant outcomes

- Treatment – Volume exchange and ATG
- 2 deaths immediately – 1 ? rejection
- 3 further late deaths
- No survival difference compared with transplants in unsensitised patients in the same period
- 50% rejection – augmented with steroids
- 22 cases antibodies present post transplant – 6 modulated in 1 month, 7 disappeared between 3-6 months, 5 remained > 6 months
- 5 cases – ‘historic-only antibodies re-appeared at some point post-transplant
- 8 cases – development of de novo DSA/non-DSA post-transplant (often rejection-associated)
- 12 cases - no antibodies detected post-transplant
- 7 cases – insufficient post-transplant samples for meaningful analysis
DSA MFI vs Rejection

**Rejection episode vs MFI**

- **Median of Rejection episode:** 1400
- **Mean of Rejection episode:** 2185
- **Range of Rejection episode:** 679-8000

- **Median of MFI:** 1121
- **Mean of MFI:** 876
- **Range of MFI:** 550-3700

- **t-test p-value:** 0.167
The next steps

- Aim is to safely facilitate increased access to cardiothoracic transplantation for sensitised patients
- Nothing is mandatory. Individual centres/laboratories can choose to adopt and adapt the Guidelines to fit local clinical and laboratory practice
- Start cautiously, assess evidence and re-evaluate approach
- How to deal with DQA and DP antibodies?
- Data from all HLAi cardiothoracic transplants in the UK are being gathered centrally, for outcome analysis (NHSBT-ODT National Transplant Database)
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