HLA Sensitisation in Renal Transplantation

Dr Fiona Regan, Consultant Haematologist

NHSBT & Imperial College Healthcare NHS Trust

- on behalf of the National Working Group on HLA sensitisation in renal transplantation

Background

1. Transplantation is the treatment of choice for patients with end-stage renal disease (ESRD)
2. HLA sensitisation is a major barrier to a successful outcome
   - **PRE-TRANSPLANT -** increased difficulty in finding a compatible donor (long wait times and for some prevention of transplantation)
   - **POST-TRANSPLANT** - inferior allograft outcomes (graft failure)
3. Blood transfusions are a recognised cause of HLA antibody sensitisation
4. Anti-HLA antibody development is not prevented by leucodepletion or red cell washing
   - Depleted unit contains $<5x10^6$ leucocytes
   - HLA Class I molecules expressed on *red cells* at low levels (100-2000/cell), but $x10^9$ in a unit

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Background

Post-transplant blood transfusions (PTBT) - shown to be associated with de novo *kidney donor specific HLA antibodies* (DSA) and HLA antibody mediated rejection (AMR)

DSA and AMR are associated with reduced allograft survival

Study	Time period	PTBT (Leucodepleted; Y/N)	DSA Development/ Outcomes
Scornik et al. *Transplantation, 2009*	2000 - 2005	746 patients; 45% transfused (No LD)	20% of patients who produced a NDSA were transfused, as opposed to 57% who produced a DSA, p=0.005
Fidler et al. *Human Immunology, 2013*	2003 - 2007	111/258 (43%) (Yes)	Pre + PTBT: greater risk of developing AMR (HR 13.9) and graft loss (HR7.1)
Ferrandiz et al. *AJT, 2016*	2008 - 2012	250/390 (64.1%) (Yes)	Transfused group: de novo anti-HLA antibodies and de novo DSA (p<0.0001)
Verghese et al. *Pediatr Transplantation, 2016*	1984 – 2013	208/482 (44%) (Yes)	Sub-analysis (n=82) transfused <1/12: no increase in DSA [HR 0.9, 95% CI 0.6-1.4, p=0.65]
Bynum et al. *Transfusion, 2018*	2004 - 2015	182/244 (74.6%) (Yes)	HLAi transplant: transfusions were not associated with increased risk of AMR

Background: Hassan et al, AJT, 2019

Q: Are HLA Ab's made to HLA antigens on blood transfused? Or does transfusion "stir up" immune system, resurging previous HLA Ab's? Difference: would HLA matched red cells prevent this, or not.

HLA typed the blood donors of transplant recipients transfused post-transplant (PTBT).

Aims:

1. Determine whether an HLA Ab is made against a blood donor post-transplant (=development of a de novo transfusion specific antibody [**TSA**])
2. Explore relationships between the development of HLA Abs common to both a blood donor and the kidney donor (ie: **TSAs and DSAs** of shared HLA specificities: **TSA=DSA**)
3. Analyse the effect of HLA Abs on clinical outcomes

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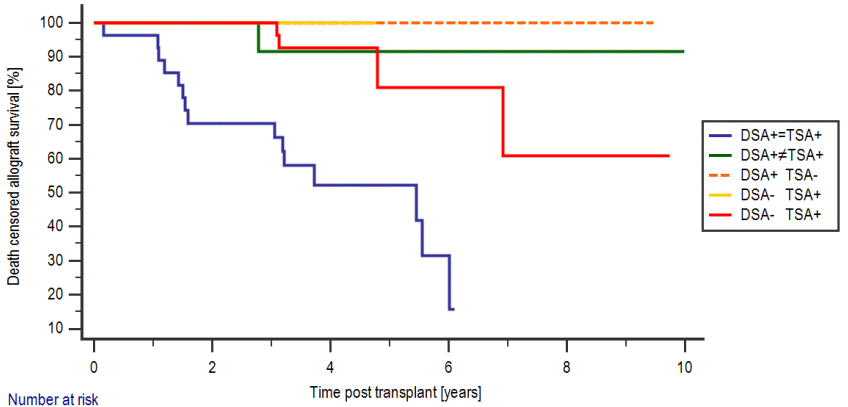
Hassan et al, AJT, 2019 - Results

- HLA sensitisation from PTBT associated with inferior allograft outcomes
- When blood transfusions share HLA antigens with the kidney donor, *de novo* HLA antibody formation is common (& outcomes worse).

- Highlights importance of:
  - **Avoiding/minimising transfusions**
  - **Avoiding shared donor antigens - Role for HLA selected blood for some?**



Number at risk						
DSA+=TSA+	28	19	9	2	0	0
DSA+≠TSA+	12	12	11	5	3	0
DSA+ TSA-	6	6	4	2	1	0
DSA- TSA+	3	3	1	0	0	0
DSA- TSA+	37	35	17	4	3	0

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HLA Matched red cell working group

↑ requests from clinicians for HLA matched red cells

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The results of our study/debate in the literature

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Formation of the HLA matched red cell Working Group

NHSBT H&I – Andrea Harmer, Colin Brown;

Clinical – Fiona Regan, Mike Murphy, Edwin Massey;

Renal – Michelle Willicombe, Sevda Hassan, Nick Torpey (BTS rep);

Statistics – Lisa Mumford (Head of ODT Studies)

MAIN OBJECTIVE: address question whether or not HLA matched red cells for transplant patients is justified (& how could do it).

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Multi-centre study of the incidence of blood product transfusion & impact on transplant outcomes

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Aims

Unclear how PTBT impacts our renal transplant population - as transfusion rates in UK transplant units are not known.

Collaborative study (NHSBT, BTS and the National Working Group):

- Aim: review incidence of blood transfusion and impact on 1-year allograft outcomes.

Methods:

1. 4 UK transplant centres participated - Cambridge; Guys; Imperial; Oxford.
2. Patients transplanted between April 2016-2017 were analysed.
3. The Hospital Tx Lab at each hospital identified transfusions received for each individual (one month before, to 1 year post transplant)
4. NHSBT statistical department collated the data and analysed the outcomes

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Post-transplant transfusions

- 723 kidney only transplants were included
- 221/723 (31%) were transfused
  - 189 (26%) blood alone
  - 7 (1%) platelets alone
  - 25 (3%) both blood and platelets
- The median time to transfusion was 4 (0-12) days
- Of those transfused, the median number of blood and platelets transfused was 2 (2-5) units and 1 (1-3) pools respectively
- Of note – on survey just before, most centres underestimated their Tx rates (10-30%)

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Conclusions

1. The current transfusion rates are comparable amongst the four units
2. Blood alone is most commonly transfused
3. The time to transfusion is acute (0-12 days) and associated with DGF
4. Transfusions are associated with inferior patient and allograft outcomes.

   At 1 year, transfusions are independently associated with:

   a. Inferior patient survival
   b. Inferior allograft survival
   c. Inferior allograft function

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Plan:

1. **Transfusion Rates** –
   a) Publications on survey (estimated Tx rates) of all renal transplant units; & of 4 Pilot Sites' actual Tx rates (& outcomes) – to raise awareness (months);
   b) Offer audit tool of *actual* Tx to all sites beyond 4 pilot sites;
   c) Repeat in:
      i. Paediatric transplants;
      ii. Pancreatic transplants; (leads for both nominated)
   d) Review guidelines – strengthen EPO advice.

2. **HLA matched blood question:**
   a) Repeat HLA sensitisation study in patients on Wait List for renal transplants (? more Ab formation)
   b) Working with DH Health Economics Analyst – on modelling of size of donor panel for HLA matched blood / HLA antigen avoidance (for future 2nd transplants etc); timing; other requirements (ABO & D matched as well).
   c) In liaison with Australia re: studies; panel logistics / practicalities and Health Economics.

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