Transplantation of highly sensitized patients based on acceptable HLA mismatches

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Preformed donor specific HLA antibodies lead to hyperacute rejection


The introduction of a serological crossmatch and exclusion of donors toward which the patient has preformed antibodies, will prevent hyperacute rejection.
Problem for the hyperimmunized patient.

Broadly reactive HLA antibodies due to previous sensitizing events

• They have often a positive serological crossmatch or donor specific HLA antibodies: contra-indication for transplantation.

• Therefore, these patients accumulate on the waiting list.
Waiting time in the UK in relation to sensitization

Fuggle et al. 2015
Options for highly sensitized patients

- Transplantation with an HLA identical or compatible donor.

- Do not accept that the patient is sensitized to the donor and try to remove the antibodies (desensitization).

- Accept that the patient is sensitized and try to facilitate allocation of crossmatch negative donor kidneys i.e. paired kidney donation.
This is also the basis of the acceptable mismatch program, implemented in Eurotransplant next the standard kidney allocation system (ET-KAS).
The ET acceptable mismatch (AM) program

**Principle:**
Identification of those HLA antigens toward which the patient did not made antibodies and use this knowledge for donor selection

**Procedure:**
- Identification of acceptable antigens by a variety of cell based and solid phase assays.
- Acceptable antigens are added to the HLA phenotype of the patient in order to identify compatible donors.
- Mandatory shipment of a kidney to the AM patient if a compatible donor organ becomes available.
Positive identification of acceptable mismatches in current and historical sera:

From the very beginning:

• Consider the HLA type of negative panel donors in CDC screening.
• Antibody screening against a patient specific panel (donors with a single HLA-A or -B mismatch), from a pool of 20,000 HLA typed blood donors.
• Testing patient’ serum against cells expressing only one HLA allele (SALs)

More recently:

• Register negative reactions in solid phase assays
• Use of computer algorithms (i.e. HLAMatchmaker)
Combination of patient HLA and AM predicts negative crossmatch

Highly sensitized

Patient HLA:  A24 A31; B27 B51; DR4

Suitable kidney donors:
A24, A31; B27, B51; DR4
Inclusion in the AM program increases the chance to receive a transplant.
Graft survival compared to patients transplanted via standard ET-KAS

<table>
<thead>
<tr>
<th></th>
<th>ET-KAS</th>
<th>AM</th>
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<tbody>
<tr>
<td>First transplant</td>
<td>42227 (85.1%)</td>
<td>250 (28.8%)</td>
</tr>
<tr>
<td>Retransplants</td>
<td>7377 (14.9%)</td>
<td>619 (71.2%)</td>
</tr>
</tbody>
</table>

Heidt et al. Kidney Int. 2017
Graft survival in re-transplant recipients

Selection:
- ≥ 1996
- Renal only
- Deceased donor
- ≥ 1 HLA antigen mm
- Re-transplant

Heidt et al, Kidney Int, 2017
Positive identification of acceptable mismatches leads to a better graft survival than avoidance of unacceptable mismatches.

Selection:
- ≥ 1996
- Renal only
- Deceased donor
- ≥ 1 HLA antigen mm
- Re-transplant

![Graph showing graft survival over time post-transplantation.](Heidt et al. Kidney Int. 2017)
How about gender balance?

**Current AM waiting list**

- Females: 263
- Males: 245

**AM patients transplanted**

- Females: 601
- Males: 408

Note: ETKAC waiting list 39% females
Graft survival in female recipients is at least as good as in males.
Female donor grafts have a significantly poorer survival
Highly sensitized patients within ET benefit from transplantation via AM program

Multivariate analysis (Cox regression)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
<th>P-Value</th>
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<tbody>
<tr>
<td><strong>A-B-DR mm</strong></td>
<td></td>
<td></td>
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<tr>
<td>1,2,3 (ref)</td>
<td>1.32</td>
<td>1.047</td>
<td>1.671</td>
<td>0.019</td>
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<tr>
<td>4,5,6</td>
<td></td>
<td></td>
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<tr>
<td><strong>Tx Period</strong></td>
<td></td>
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<tr>
<td>1996-2005 (ref)</td>
<td>0.64</td>
<td>0.522</td>
<td>0.790</td>
<td>&lt;0.001</td>
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<tr>
<td>2006-2015</td>
<td></td>
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<tr>
<td><strong>Donor sex</strong></td>
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<tr>
<td>Female (ref)</td>
<td>0.82</td>
<td>0.682</td>
<td>0.987</td>
<td>0.036</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Recipient age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50 (ref)</td>
<td>0.79</td>
<td>0.640</td>
<td>0.971</td>
<td>0.025</td>
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<tr>
<td>&gt; 50</td>
<td></td>
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<tr>
<td><strong>Donor age</strong></td>
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<tr>
<td>≤ 50 (ref)</td>
<td>1.73</td>
<td>1.438</td>
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<td>&lt;0.001</td>
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<td>&gt; 50</td>
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<td><strong>Tx via AM</strong></td>
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<tr>
<td>No (ref)</td>
<td>0.72</td>
<td>0.576</td>
<td>0.903</td>
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<tr>
<td>Yes</td>
<td></td>
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Heidt et al. Kidney Int. 2017
In contrast to ET-KAS allocation, no HLA match effect in acceptable mismatch (AM) transplants.

Heidt et al., Transplant Immunol 2015
Is the lack of a match effect in AM patients due to a lower number of antibody epitopes on acceptable mismatches?

Every HLA allele has many polymorphic positions

All yellow amino acids configurations are potential targets for antibodies.
Average number of amino acid differences on donor HLA mismatch is only slightly lower in acceptable mismatch transplants.
No effect of epitope matching in acceptable mismatch transplants.

Immunized single HLA antigen mismatched retransplants

Heidt et al. 2018
Identification of acceptable epitopes might enable prediction of additional acceptable mismatches.
Definition of actual antibody epitopes is work in progress.

http://epregistry.ufpi.br

Description

This website is designed for research purposes only. The contents are not intended for making clinical decisions regarding donor selection or patient care.

There are five separate databases: ABC, DRB1/3/4/5, DQB + DQA, DPB + DPA and MICA.

Their layouts display:

1. Epitope names
2. Polymorphic residue descriptions
3. Epitope frequencies
4. Antibody reactivity descriptions of "confirmed" or "provisional" antibody-verified epitopes
5. Information about corresponding "structural" epitopes
6. Epitope-carrying alleles in Luminex panels
7. Listings of all alleles with antibody-verified epitopes.

Each epitope has its own row and epitopes are sorted according their sequence positions. Under each epitope there are rows for possible variants with distinct molecular configurations. Each epitope database has search options to identify repertoires of antibody-verified epitopes on selected alleles and epitopes that are mismatched for a given HLA type. For more detailed information about the HLA Epitope Registry, click here.
• The acceptable mismatch (AM) program has proven to be an efficient tool to enhance transplantation of highly sensitized patients.

• However, a proportion of the patients, especially those with rare HLA types in relation to the donor population, remain on the waiting list.

• Options for these patients:

  Desensitization: removal of donor specific antibodies.

  A larger donor pool: a Europe wide acceptable mismatch program.
EUROSTAM: A EUROpe-wide Strategy to enhance Transplantation of highly sensitized patients on basis of Acceptable HLA Mismatches.

Question:
Can we increase the chance to receive a compatible donor by extension of the donor pool for highly sensitized patients, who have hardly any chance to be transplanted in their own organization?

Approach:
Simulation studies on basis of the HLA phenotypes of the actual deceased kidney donor populations of the participating countries and organizations: Czech Republic (Tony Slavcev), Greece (Aliki Iniotaki), Spain (Jaume Martorell), UK (Sue Fuggle) and Eurotransplant.

ET patients included:
Patients included in the AM program and waiting for more than 2 years.
• Number of long waiting highly sensitized patients: 121

• Patients that benefit from a different donor pool: 27 (22%)
  - 19 patients 1% increase
  - 5 patients 2% increase
  - 2 patients 4% increase – Barcelona donor pool
  - 1 patient 5% increase – UK donor pool

Mumford et al. 2017
Simulation showed that more than 25% of the patients have a better chance to find a suitable donor in another population.

Study included 720 patients from Eurotransplant, UK transplant, Czech Republic, Greece and Barcelona. For 188 of them extension of the donor pool was beneficial.
Conclusions

• The acceptable mismatch program is an excellent tool to enhance successful transplantation of highly sensitized patients.

• Positive identification of acceptable mismatches is superior over avoidance of unacceptable HLA mismatches

• The lack of an HLA antigen or epitope matching effect suggests a different immune regulation to acceptable mismatches

• Knowledge of acceptable epitopes will be beneficial for the search of additional acceptable mismatches.

• Extension of the donor pool will be of benefit for patients with rare HLA phenotypes in relation to the own donor population.
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