CHAPTER 5.2 Kidney transplantation in highly sensitised patients

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1 Introduction

Sensitisation against human leukocyte antigen (HLA) can be induced by pregnancy, blood transfusion, or a previous transplant. In the Eurotransplant (ET) allocation system, high sensitisation is defined by a panel-reactive antibody of at least 85% (traditionally in CDC-based tests; later extended to solid phase assays, provided that the HLA specificities can be attributed to an immunising event). Highly sensitised patients are disadvantaged because of their broad immunisation status that results in positive crossmatches with many kidney donors, precluding a transplantation in those cases of organ offer. There are several strategies that can help highly sensitised patients access to a more timely transplantation, including desensitisation to reduce the amount of pre-existing, circulating antibodies to a level that allows successful transplantation from a deceased or living kidney donor; participation in kidney paired donation (KPD) or transplantation within the ET Acceptable Mismatch (AM) programme.

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2 Pre-transplant identification of high-risk patients

The HLA sensitisation of a potential transplant recipient is assessed prior to waitlisting, at regular time intervals thereafter, and after every immunising event. The objective is to measure the degree of HLA sensitisation and to identify HLA specificities that are targets of the patient's antibodies. Although transplant centres vary in their approach to measuring HLA sensitisation, all assess for the presence of HLA antibodies by testing patient sera in solid phase assays (using microbeads with attached HLA antigens) and in cellular assays (using a lymphocyte panel in a complement-dependent cytotoxicity (CDC) test). At our centre, in addition to CDC antibody screening, we perform mixed and single antigen bead assays (One Lambda) on a Luminex platform to screen for and characterisation of HLA antibodies, respectively [1]. Antigens against which antibody reactivities are detected either in CDC or in Luminex at a mean fluorescence intensity (MFI) of at least 5,000 (for patients without known history of allosensitisation) or 3,000 (for pre-sensitised patients) are designated as 'unacceptable antigens'. These unacceptable antigens are then entered into ENIS, the ET computer system used for organ allocation. If a patient has an unacceptable antigen listed in ENIS, kidneys from donors carrying that antigen will not be offered to the patient. A calculated panel-reactive antibody (cPRA), also called virtual PRA (vPRA) in the ET nomenclature, is then computed based on the patient's unacceptable antigens. Panel-reactive antibodies (PRA) estimate the percentage of the donor population against which the patient has antibodies and characterise the breadth of HLA sensitisation. Higher PRA is associated with lower chances of compatible transplantation and inversely correlates with the likelihood of an HLA compatible donor match. It should be noted that MFI levels can vary by approximately 20–25% between HLA laboratories and that the MFI threshold levels used to define an unacceptable antigen are not standardised across transplant centres. ET uses the term "non-sensitised" for patients with a vPRA of 0%. At our centre, patients with a vPRA of at least 30% are considered having an increased immunological risk and may be eligible for desensitisation treatment. We further stratify the immunological risk based on the number of transplant (first or retransplant), the presence of donor-specific antibodies (DSA) against the organ offer and the combination of other immunological test results (see section 3.1).

3 Assessment of the sensitised transplant candidate

The approach varies depending on whether the transplant candidate has a potential living donor. For sensitised patients with one or more potential living donors, we first perform antibody screenings and a virtual crossmatch to determine whether the patient has donor-specific anti-HLA antibodies (DSA). In addition, we perform a physical crossmatch (CDC crossmatch) with T, B and unseparated lymphocytes. The laboratory test results help us evaluate the potential risk of antibody-mediated rejection (AMR) and, if appropriate, consider desensitisation therapy, or advise against transplantation with the donor tested. All sensitised patients with a potential living donor are also listed for a deceased donor transplant.

Patients with a negative CDC crossmatch may be DSA negative or positive (that means, in the absence or presence of DSA in Luminex single antigen bead assays). This includes patients with a history of DSA that were not detectable at the time of testing above a defined MFI cut-off, which is a common scenario because DSAs can wane over time and/or fluctuate above and below the level of detection. Furthermore, patients may have memory B cells that can re-emerge upon antigen stimulation. For example, mothers may have been exposed to foreign HLA antigens in pregnancies and can mount a memory response when receiving a transplant from their child or their husband, although DSA were not detectable during antibody screening. Therefore, pre-sensitised patients with a negative CDC crossmatch are at risk of developing acute and/or chronic AMR, especially if low levels of DSA are present. We perform peri-operative desensitisation in these cases. For sensitised patients (vPRA ≥ 30%) without a potential living donor, we register them for the deceased-donor transplant list and offer pre-transplant desensitisation once an HLA incompatible, but otherwise acceptable organ offer is available (see section 4.2).

3.1 Assessment and classification of sensitised transplant candidates in Heidelberg

Patients are classified in four immunological risk categories based on their pre-transplant immunological work-up.

Risk category	Criteria (the presence of at least one criterion is sufficient)	Immunosuppressive therapy
High risk	• CDC PRA > 85% • Positive reactivity in the Luminex screening test for both class I and class II HLA antigens • In candidates for re-transplants, positive reactivity in the Luminex screening test for class I only • In candidates for re-transplants, positive reactivity in the Luminex screening test for class II only plus a positive B cell CDC crossmatch	See section 4.2
Intermediate high risk	Low level DSA that were not listed as unacceptable antigens (= DSA with MFI value < 3000 in patients with known allosensitising events; or < 5000 (in patients without previous allosensitisation)	Thymoglobulin, tacrolimus, MMF, steroids • pre-Tx: 1 x plasma exchange • post-Tx: 2 x plasma exchange
Intermediate low risk	vPRA > 30%, no detectable DSA (defined by using an MFI cutoff of 1,000)	Thymoglobulin, tacrolimus, MMF, steroids
Low risk	vPRA ≤ 30%, no detectable DSA (defined by using an MFI cutoff of 1,000)	IL2-receptor antagonists, Tacrolimus, MMF, steroids

The MFI values are measured with One Lambda Luminex test kits and may not be applicable to the Luminex kits from other vendors.

4 Pre-transplant desensitisation

The overall goal of HLA desensitisation is to increase the likelihood of a successful kidney transplant in patients with extensive HLA antibody sensitisation and to prevent post-transplant AMR in these patients. Desensitisation can be performed on patients awaiting either a living or deceased donor transplant. While the objectives are similar in both contexts, the approach may differ due to the unpredictable timing of deceased-donor transplantation in relation to the administration of desensitisation therapy. Although there is no universally accepted HLA desensitisation protocol, the most commonly used protocols employ

a combination of the following strategies: (i) Immunomodulation of the recipient's immune system, typically with intravenous immunoglobulins (IVIG); (ii) B cell depletion, most commonly with the anti-CD20 monoclonal antibody rituximab; (iii) removal of circulating HLA antibodies, typically with extracorporeal methods such as plasmapheresis or immunoadsorption.

4.1 The Heidelberg approach to desensitisation

HLA desensitisation strategies vary between transplant centres, depending on clinical experience and preference. There is a lack of high-quality data in the form of randomised controlled trials comparing existing desensitisation approaches, and the optimal therapy remains undefined. The most critical components of an integrative approach are pre-transplant identification of high-risk patients on the waiting list (see Section 3.1) and risk-stratified organ allocation. For instance, patients with a high vPRA and/or positive results for both class I and II HLA antibodies in the Luminex antibody screening test are at an increased risk of graft loss. Such patients can be successfully and promptly transplanted if there are only a few HLA mismatches [2] or the transplantation is facilitated via the Eurotransplant Acceptable Mismatch Programme, which allocates organs to highly immunised patients with high priority [3].

All patients categorised as high risk receive apheresis treatment (one session pre-operatively and at least six sessions post-operatively until serum creatinine falls below 2 mg/dL and DSA become undetectable) during a deceased-donor organ offer process or in preparation for transplantation from a living donor. This treatment is used to reduce the level of potentially undetected antibodies and prevent an acute antibody-mediated allograft injury due to an early rebound of pre-existing DSA. To prevent the development of *de novo* DSA, apheresis is combined with the administration of the anti-B cell antibody rituximab. B cells are important antigen-presenting cells that are critical for T cell activation and the development of T cell memory during alloimmune responses. Despite having no effect on long-lived plasma cells, anti-CD20 therapy has been associated with a reduction in DSA reactivity in some reports. Rituximab may prevent antibody-producing cells from being generated from the naïve B cell pool and may target short-lived plasma cells that express CD20 on their surface. In addition, anti-CD20 therapy may deplete B cell aggregates within allografts. High-risk patients also receive T cell-depleting induction therapy with thymoglobulin, which targets an early T cell response that would support the development of

de novo DSA. The Heidelberg Algorithm for diagnosing AMR in the early stages after successful kidney transplantation involves protocol biopsies on days 7 and 90, as well as post-transplant antibody monitoring.

Post-transplant antibody monitoring has been refined further with the introduction of the C1q assay. DSA with MFI greater than 3000 can be further tested for the presence of C1q-binding capacity. According to some reports, the appearance of C1q-binding DSA post-transplant can be considered a major risk factor for graft loss due to AMR [4, 5, 6].

4.2 Desensitization protocol for patients at high immunological risk on the *deceased donor* waiting list

See section 3.1 for definitions of high immunological risk.

1. A serum is taken before (and, optionally also after) plasmapheresis for a prospective CDC crossmatch.
2. Plasmapheresis (exchange volume = 2 times plasma volume; substitute with fresh frozen plasma [FFP] and citrate anticoagulation).
3. If the CDC crossmatch is negative (T lymphocytes, B lymphocytes, unseparated lymphocytes without and with DTT), administer Thymoglobulin® (dose: 1.5 mg/kg), followed by rituximab (dose: 375 mg/m²). Kidney transplantation can then be performed. *Caution:* Since 200 mg/m² of methylprednisolone is administered for desensitisation prior to Thymoglobulin administration, only 100 mg/m² of methylprednisolone is given intraoperatively instead of the usual dose of 300 mg/m².
4. If the CDC crossmatch with either serum (pre- or post-plasmapheresis) is positive, kidney transplantation cannot be performed.
5. Tacrolimus, MMF and methylprednisolone are administered according to the standard regimen.
6. Following surgery, a further 2–3 doses of Thymoglobulin® are administered, with the dosage adjusted according to the total lymphocyte count (target: 100/µl).
7. Postoperatively, plasmapheresis or immunoadsorption is performed until transplant function stabilises, i.e. until serum creatinine falls below 2 mg/dL, GFR exceeds 30 mL/min/1.73 m² and DSA is less than 1,000 MFI. This process continues for at least six treatment sessions in the first two weeks post-transplant.

8. Prophylaxis against infection with cotrimoxazole for 12 months and valganciclovir as indicated.
9. Protocol biopsies are performed on days 7 and 90 post-transplant.
10. Perform an indication biopsy in the event of deterioration in graft function, an increase in pre-existing DSA and/or the development of *de novo* DSA.
11. Monitor DSA on days 0, 7, 30, 180, and then every six months, as well as on the intermediate days between plasmapheresis sessions initially.

4.3 Desensitisation protocol for patients at high immunological risk with a *living donor*

See section 3.1 for definition of high immunological risk.

1. At least six immunoadsorption sessions (Globaffin column, Fresenius) should be performed prior to transplantation. ACE inhibitor therapy should be discontinued one week beforehand. Immunoadsorption is performed on alternate days. Further postoperative immunoadsorption may be necessary until the serum creatinine level falls below 2 mg/dL, the GFR is greater than 30 mL/min/1.73 m^2, and the DSA is less than 1000 MFI.
2. DSA are determined on the days when no immunoadsorption takes place. If DSA reactivities are reduced below 1000 MFI, transplantation can be performed and has to be carried out as soon as possible due to potential DSA rebound.
3. Immunosuppressive therapy involving tacrolimus, mycophenolate mofetil (MMF) and methylprednisolone (24 mg/m^2 intravenously in the morning) should be started one week prior to transplant surgery.
4. Thymoglobulin® is administered preoperatively at a dose of 1.5 mg/kg.
5. Subsequently, rituximab is administered intravenously at a dose of 375 mg/m^2 pre-/intraoperatively.
6. Postoperatively, two to three further doses of Thymoglobulin® are administered, adjusted according to the total lymphocyte count (target: 100/µl). *Caution:* Since 200 mg/m^2 of methylprednisolone is administered prior to Thymoglobulin® administration, only 100 mg/m^2 is given intraoperatively.
7. Oral methylprednisolone is administered according to the standard regimen.
8. Prophylaxis against infection with cotrimoxazole (for 12 months) and valganciclovir (as indicated).

9. Protocol biopsies are performed on days 7 and 90 post-transplant.
10. Indications for biopsy include deterioration of graft function, an increase in pre-existing DSA and/or the development of *de novo* DSA.
11. Monitor DSA on days 0, 7, 30, 180 and then every six months. Initially, monitor on intermediate days when no immunoadsorption takes place.

5 Outcome

The decision to proceed with an HLA-incompatible kidney transplant rather than wait longer for a more suitable donor is often difficult, especially given the increased mortality observed among adult dialysis patients compared with transplant recipients [7]. In virtually all patient populations, the long-term risk of death is lower with a kidney transplant than with dialysis [8, 9]. A large multicentre study of 1,025 recipients of an HLA-incompatible living-donor kidney transplant found higher short- and long-term (up to eight years) patient survival rates among recipients of an HLA-incompatible transplant compared with matched controls on the waiting list [10]. Overall, however, a greater degree of HLA incompatibility is associated with a higher risk of graft loss and death. A positive flow or cytotoxic crossmatch was found to be associated with a 1.65- and 1.80-fold higher risk of graft loss, and a 1.32- and 1.51-fold higher risk of death, respectively, compared with HLA compatible recipients [11]. This study found that five-year unadjusted graft loss was 17%, 20%, 29%, and 40% for HLA compatible recipients, recipients with DSA but a negative flow crossmatch, recipients with a positive flow crossmatch but negative cytotoxic crossmatch and recipients with a positive cytotoxic crossmatch kidney transplant, respectively. The five-year unadjusted mortality rate was 9%, 10%, 13%, and 19% for HLA-compatible recipients, recipients with DSA but a negative flow crossmatch, recipients with a positive flow crossmatch but negative cytotoxic crossmatch, and recipients with a positive cytotoxic crossmatch kidney transplant, respectively.

In Heidelberg, we found that our approach can be used to transplant high-risk sensitised patients with graft survival rates similar to those of non-sensitised kidney recipients. In 28 adult recipients of deceased donor kidneys, the one-year graft survival rate, death-censored graft survival rate, and patient survival rate were 92%, 96%, and 96%, respectively. No graft loss or patient death was observed in the six living donor kidney recipients [12]. AMR occurred in one living and two deceased donor kidney transplant recipients during follow-up. This

therapy was accompanied by rigorous infection prophylaxis with valganciclovir when the donor is CMV-positive and cotrimoxazole in all patients.

There are few published reports on the outcome of desensitisation protocols in paediatric kidney transplant recipients. One UK study reported that, of 711 living donor kidney transplants performed in the UK, six were HLA-incompatible [13]. At a median follow-up of 6.8 (3.6–14.0) years, patient survival was 100% and 96% in the HLA-incompatible and HLA-compatible groups, respectively. Death-censored kidney allograft survival was 100% in both groups at the final follow-up. There were no cases of primary non-function in the HLA-incompatible group, compared to 2% in the HLA-compatible group. The authors concluded that HLA-incompatible kidney transplantation is a feasible option for paediatric recipients when no compatible donors are available. However, an increasing degree of incompatibility is overall associated with a higher risk of graft loss. Data on infection-related complications in this population are limited, with some studies showing similar overall infection rates to those of average transplant recipients.

6 Investigational approaches

Several investigational therapies are being evaluated for use in desensitisation regimens. One such therapy is imlifidase, an IgG-degrading enzyme derived from Streptococcus pyogenes. This recombinant cysteine protease cleaves all four subclasses of human IgG into F(ab')2 and Fc fragments, thereby inhibiting complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity. Imlifidase has received conditional approval from the European Medicines Agency (EMA) for use in desensitisation procedures for adult kidney transplantation within the European Union (so far not for paediatric patients). It is not yet approved by the US Food and Drug Administration (FDA) for use in the United States. Three-year outcomes were reported in an analysis that pooled adult patients from four open-label phase II studies [14]. Of the 39 patients who underwent a positive crossmatch kidney transplant, 15 (38%) experienced AMR. Overall three-year graft survival was 84%; among patients who experienced AMR, three-year graft survival was 93%, compared to 77% among those who did not. Among the 13 patients with vPRA of at least 99.9%, who were considered unlikely to have been transplanted under conventional protocols, three-year graft survival was comparable with that of the overall study population (92%) after receiving a positive crossmatch deceased-donor allograft.

However, seven of these patients (54%) experienced AMR within six months of the transplant, although none of the graft losses were attributed to AMR. Overall, the initial experience with imlifidase is encouraging, suggesting that it can facilitate HLA incompatible transplantation, although further research is required.

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