Idefirix® (Imlifidase): A Paradigm Shift in Transplanting the Untransplantable?

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Meeting Summary

This symposium took place during the 2021 virtual meeting of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). Heemann opened the session by highlighting the numbers of patients waiting for a kidney transplant and the proportion that will never receive an organ offer under the current system.

Morath defined the term untransplantable as highly sensitised (HS) patients with only a very small chance of receiving a crossmatch (XM) negative organ during allocation or when on a waiting list for organ allocation. These patients face extended times on waiting lists and are often removed from the list or die. Current organ allocation systems cannot fully address this issue, meaning that for some patients there is no hope of transplantation. There is a need for an alternative option that combines a special organ allocation scheme together with desensitisation options to remove donor-specific antibodies (DSAs), thereby increasing the chance of a donor organ offer.

Oberbauer outlined the current transplant options for HS patients, which are limited to live kidney paired exchange, acceptable mismatch, or desensitisation. Existing desensitisation protocols have demonstrated variable efficacy and the majority are only for use in a live donor setting.

Lorant introduced Idefirix® (imlifidase) as a new option for desensitisation of adult patients with positive XM against a deceased kidney donor. He highlighted results from clinical trials that showed that imlifidase treatment rapidly inactivated DSAs and converted positive XMs into negative, with 2 year patient and graft survival of 90% and 82%, respectively.

How Can We Transplant Highly Sensitised Patients?

Uwe Heemann

Germany alone has approximately 7,000 people waiting for a kidney transplant. In 2020, there were nearly 600 HS patients on the waiting list (5.5% of listed patients) and nearly 280 transplantable patients in the Eurotransplant Acceptable Mismatch (AM) programme.[1]

There are patients in the AM programme who cannot be transplanted at present. The EUROSTAM initiative investigated the possibility of transplanting all comers, including HS patients. An analysis of the Eurotransplant database, including the UK, Spain, Czech Republic, and Greece in 2012–2015, identified 700 patients who were not transplantable.[2] If the AM programme of Eurotransplant was enlarged, 25–30% would benefit but 400 patients would still never receive an organ offer. This translates into 0.5% of those waiting for a transplant never receiving an organ offer, making it clear that help is needed. This symposium addressed the question "Is imlifidase the solution we need?" in three talks.

Defining the Untransplantable

Christian Morath

Untransplantable refers to HS patients with only a small chance of getting a XM negative organ during organ allocation. Traditionally, these patients were defined by a panel reactive antibody (PRA) of ≥85%. But more recently, with the introduction of virtual PRA (vPRA), patients with vPRA ≥95–98% were considered strongly disadvantaged and potentially untransplantable.

Examination of the Heidelberg waiting list revealed that 9.1% of patients had vPRA >85% and 6.3% had vPRA >95%, which represents a considerable proportion of the total waiting list. These are highly disadvantaged patients. Two case reports with vPRA ≥99% illustrate this point; both had a very low donor frequency (0.044% and 0.160%) and had been waiting for 16 and 10 years, respectively. These patients will never be transplanted unless additional measures are taken, such as desensitisation.

Looking at the broader Eurotransplant area, there are special initiatives for HS patients such as the AM programme. In the past, patients with a PRA >85% were transplanted with high priority. This programme helps to avoid long waiting times in sensitised patients and is associated with good graft survival rates in transplanted patients.[3] A study in 2018 showed that graft survival rates at 10 years for patients in the AM programme (n=869) were similar to patients with PRA 6–85% (n=12,289) but better than those with PRA >85% (n=1,866) transplanted outside the AM programme.[1] However, two points should be considered. First, patients transplanted in the AM programme in this analysis had a current PRA of only 26%, indicating that they were perhaps not the most disadvantaged. Second, the analysis only included patients who were successfully transplanted. There were no data on patients who were placed on the AM but received no donor organ.

The study leads to the question: what are we currently looking at and what should we be looking at? Currently, we are looking at graft survival rates of patients who received a kidney transplant. Just 57.6% of patients placed on the AM waiting list during the last 28 years received a successful transplant.[4] However, 42.4% of AM patients were not transplanted. We should be looking at patient survival rates of patients placed on the waiting list rather than survival rates of those who received a transplant.

What happened to the patients who were not transplanted? The EUROSTAM project provides a picture of the fate of these patients. The project compared access to transplantation for HS patients from the local donor population (e.g., Eurotransplant) versus a larger donor pool comprising different partner organisations of Eurotransplant (i.e., the UK, Spain, Greece, the Czech Republic). For this simulation, 722 patients were identified from the five organisations with ≥95% sensitisation and a waiting time >5 years (i.e., the untransplantable patients). Even with broadening the donor pool, 73% of patients had no greater chance of getting a compatible organ offer.[5] These data illustrate that the problem extends beyond Heidelberg and that across Europe many patients accumulate on the waiting list without a realistic chance of an organ offer unless additional measures such as desensitisation are taken.

Looking into the situation in the USA, there was some improvement in 2014 after implementation of the kidney allocation system (KAS). For HS patients, there was a steep increase in the transplantation rate from around 2–3% to 17%.[6] However, 34% of HS patients have a calculated PRA (cPRA) of ≥99.95% and these patients did not benefit from implementation of the KAS with transplantation rates of only 8%. This group makes up a considerable proportion of the waiting list, with 5.5% of the total list having a cPRA of 100%.[7] These patients are mostly younger (48.0 years), more likely retransplant recipients (71.8%), and are more likely to have longer waiting times (4.3 years). This illustrates that in the USA, there is also a considerable proportion of patients who need additional measures such as desensitisation to obtain access to kidney transplantation.

What happens to patients with no realistic chance of getting a kidney transplant and a suitable organ offer? An analysis of waiting times in the UK stratified by calculated reaction frequency (cRF) levels showed that most patients wait <7 years.[5] However, if the cRF value is >95%, patients wait up to 35 years. Data from the USA illustrate that only a very small proportion of patients (<10%) with very high cPRA (>99.9%) are transplanted.[7] The data show that most patients persist on the waiting list, and are then removed or die.

More than 50% patients with cPRA >99.9% have been on the waiting list for >5 years compared to 10% of those with cPRA <80%.[7] In an analysis of mortality stratified by cPRA before and after implementation of the KAS programme, mortality rates up to 3 years were similar for all cPRA categories except 99.9%+ which continued to have a higher mortality rate compared to all other groups.[8]

Most HS patients cannot be transplanted by kidney allocation alone and need additional measures. Data from the USA show that increased anti-HLA DSA strength was associated with worse graft outcomes and higher mortality following live donor kidney transplantation.[9] Desensitisation therapy conferred a survival advantage compared to dialysis or transplantation or dialysis alone.[10] In the desensitisation group, the Kaplan–Meier estimate of patient survival was 80.6% at 8 years, compared with 49.1% in the dialysis or transplantation group and 30.5% in the dialysis only group (p<0.001 for both comparisons).

The combination of a special allocation programme, such as the AM programme, and desensitisation is a strategy that can lead to transplantation and good results. The introduction of an integrated algorithm in Heidelberg in 2006–2007 led to improved graft survival.[11,12] Graft survival in sensitised patients was equal to that of unsensitised patients. In addition, many patients who were transplanted following pre-transplant desensitisation would otherwise have persisted on the waiting list for an indefinite period of time.

In summary, all available measures are needed to transplant the (untransplantable) patients with very high PRA who make up a considerable proportion of those on the waiting list. These patients need special allocation together with desensitisation.[13] Unfortunately, most of these special programmes/measures (e.g., kidney paired donation) are not permitted in Germany.

Pathways to Transplant the Positive Cross-Match Highly Sensitised Patients

Rainer Oberbauer

For very HS patients and those without living donors, a strategy of desensitisation offers the best hope of transplantation.[14] It has been calculated by Keith et al. that to achieve a 95% probability of finding an acceptable donor, a candidate with a cPRA of 99.99% would need to be part of 30,000 potential donor match runs.[15] The probability of finding an acceptable match is calculated as 1-(cPRA)n where n is the number of potential donors. To achieve a 95% chance of finding an acceptable match, a candidate with a cPRA of 95% would need to be part of 59 donor match runs. This means that if 59 blood group compatible (e.g., blood group O) donors are available per year then it is reasonable to have these patients in an AM programme. HS patients also have a very low chance of transplantation through a paired exchange programme, and, for these patients, desensitisation is the only realistic way to proceed.

A simulation of chances for match in a kidney paired donation programme stratified by cPRA demonstrated that most matches, even in the low sensitised patients, occur in the first 3 months.[16] After this period, the number of candidates remains fairly constant.

There is some evidence showing a survival benefit from desensitisation and transplantation with a kidney from an incompatible living donor. A multicentre study from the USA demonstrated that patients who underwent desensitisation therapy and received kidney transplants from HLA-incompatible living donors had a substantial survival benefit compared with those who did not undergo transplantation and those who waited for transplants from deceased donors.[17] However, a similar analysis from the UK found no survival benefit.[18] Possible explanations for the discordant findings include different definitions of desensitisation, use of different matching methods, and different patient populations between the two studies.[19]

The most common desensitisation protocols typically non-specifically remove circulating DSA with plasmapheresis, immune absorption, or plasma filtration. In addition, the production of antibodies can potentially be inhibited by drug combinations while single drug combinations have not been shown to be successful. Desensitisation protocols have been developed based on experienced rather than on solid clinical trials since the number of patients in need of such a procedure is rather limited.

The pharmacological targets of humoral response in organ transplantation have been illustrated by Kwun and Knechtle.[20] The interaction of follicular helper cells with B cells in the lymph node can be inhibited by established therapies such as costimulation blockade and anti-B cell therapies. Plasma cells can be depleted with drugs from the myeloma field such as anti-CD38 antibodies or second or third generation proteasome inhibitors. Further targets include the unspecific removal of antibodies from the circulation and the inhibition of the complement cascade although this has not been proven to be useful for desensitisation.

A recent study in a 25-centre cohort using Scientific Registry of Transplant Recipients (SRTR) linkage showed that the risk of biopsy-confirmed acute rejection (AR) increased with sensitisation.[21] AR developed in 8.4% of compatible live donor kidney transplantation, 18.2% of positive Luminex, negative flow XM, 21.3% of positive flow, negative cytotoxic XM, and 21.7% of positive cytotoxic XM recipients.

Incompatible living donor kidney transplantations without biopsy-confirmed AR exhibited an even lower risk of graft loss as compared to compatible live donor transplants with subsequent biopsy-confirmed AR. So not unexpectedly, incompatible living donor transplants with AR had the worst results, with approximately 40% rate of graft loss at 10 years after transplantation. The findings demonstrate that biopsy-confirmed AR is an important effect modifier in that setting.

What can be done to prevent the reappearance of DSA and antibody-mediated rejection (AMR)? Dual targeting is an appealing strategy, targeting the follicular helper cell and B cell interaction with costimulation blockade and at the same time inhibiting plasma cells with proteasome inhibitors, for example.[20]

This approach has been tested in a non-human primate model of kidney transplantation.[22] The authors evaluated carfilzomib (CFZ), a second-generation proteasome inhibitor, plus the costimulation blocker lulizumab (CD28dAb), a CD28 domain antibody antagonist that selectively targets the CD28-CD80/86 interaction and preserves the co-inhibitory signal (CTLA4-CD80/86). Four weeks of perioperative desensitisation with CFZ and CD28dAb reduced DSA levels compared to untreated controls by approximately 50%. This combination also reduced follicular helper cells and proliferating B cells in the lymph node after desensitisation. CFZ and lulizumab did not prevent DSA rebound as early as 2 weeks after engraftment. The combination prolonged graft survival and prevented AMR initially; however, after 3 months all grafts failed due to AMR.

In summary, HLA-incompatible transplants lead to a broad alloimmune response as evidenced by a mixed lymphocyte reaction before transplantation, high PRAs, and potentially non-HLA alloimmunity. Thus, many branches of the humoral cascade need to be targeted. Desensitisation is a strategy for a minority of live

donor kidney transplants but is the only chance of a transplant for HS patients. Imlifidase may be an option in such situations.

Idefirix® (Imlifidase): A New Treatment Option

Tomas Lorant

Desensitisation is an effective technology that could be considered in selected patients. HS patients typically have elevated levels of numerous HLA antibodies and transplantation requires long-term removal of these antibodies.

It has been demonstrated that patients with high pre-transplant levels of DSAs have worse outcomes (e.g., lower likelihood of graft survival) after transplantation compared to those with low levels of DSAs.[23] Activation of the complement cascade is involved in AMR. It has been demonstrated that patients with complement-binding DSAs after transplantation had the lowest 5-year rate of graft survival (54%), compared to patients with non-complement-binding DSAs (93%) and patients without DSAs (94%).[24]

Data from the USA suggest that HLA-incompatible live donor kidney transplantation may improve patient survival compared to remaining on the waiting list or waiting for a compatible deceased donor kidney.[17] This indicates that in these cases, if there is an available HLA-incompatible kidney, desensitisation followed by transplantation could be of potential benefit.

Imlifidase is an immunomodulatory streptococcal protease agent that cleaves all forms of IgG in a 2-step process.[25-27] IgG is cleaved at the lower hinge region to form $F(ab')_2$ and Fc fragments. Imlifidase is highly specific for IgG, and other molecules (i.e., IgA, IgD, IgE, and IgM) are not cleaved. IgG cleavage leads to inactivation of all IgG-dependent Fc-dependent effector functions, including antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[25-29]

A number of clinical studies have been conducted with imlifidase. In a Phase I study of 29 healthy subjects, imlifidase was able to inactivate Fc-mediated effector functions *in vivo*, was considered safe with no serious adverse events, and there was no dose limiting toxicity.[25] This research was followed by four Phase II clinical studies in kidney transplant recipients.[30-33]

The first transplant was performed in a patient with a positive serum XM (HLA-B7). After imlifidase infusion, when an HLA-incompatible (HLA-B7+) kidney from a deceased donor was offered, the HLA antibody profile was negative, and the kidney was transplanted successfully.[30] Stable graft function was maintained for >36 months with normal creatinine clearance, no proteinuria, and no rejection episodes.

Jordan et al. reported the combined experience of two independently conducted open-label, Phase I–II trials assessing the efficacy of imlifidase for desensitisation and kidney transplantation from an HLA-incompatible donor.[31] A total of 25 highly HLA-sensitised patients (11 in Sweden and 14 in the USA) received imlifidase before undergoing transplantation with a kidney from an HLA-incompatible donor. Total IgG and HLA antibodies were eliminated at transplantation. Perfusion of allografts after transplantation was achieved by 24 patients. AMR occurred in 10 patients (3 in Sweden and 7 in the USA) at 2 weeks to 5 months after transplantation, but all of these patients had a response to treatment. There was 1 graft loss, which was mediated by non-HLA IgM and IgA antibodies. The authors concluded that imlifidase reduced or eliminated DSAs and permitted HLA-incompatible transplantation in 24 of 25 patients.

The Highdes trial (15-HMedIdeS-06)[33] was focused on very HS patients. This was an open-label, single arm, Phase II trial conducted at five centres in the USA, Sweden, and France. The primary efficacy endpoint was the ability of imlifidase to convert a positive to a negative XM test within 24 hours after dosing. A total of 18 patients were enrolled. DSA were present in all patients and the median cPRA was 99.83%. The majority of transplanted patients (89.5%) demonstrated conversion of baseline positive XM to negative within 24 hours after treatment with imlifidase. DSA usually rebounded 3–14 days after imlifidase therapy, although there

was substantial interpatient variability. At 6 months, patient survival was 100% and graft survival was 88.9%. AMR occurred in 38.9% patients, with an onset 2–19 days post transplantation. Of 237 total treatment-emergent adverse event, seven (occurring in six patients) could be attributed to imlifidase.

Regarding long-term follow-up, a prospective, observational, 5-year study is currently ongoing in 46 HS patients who received kidney transplants after desensitisation with imlifidase.[34] This study will provide data on parameters such as patient and graft survival, comorbidity, treatment of graft rejection episodes, quality of life, and anti-drug antibody levels and runs until December 2022.[35]

Two-year results in 31 patients demonstrated a survival rate of 91% (31 of 34 patients).[34] The three deaths all occurred in the positive XM population (i.e., the most complex patients) at 7–12 months post-transplantation and were not related to imlifidase treatment. At 2 years, death-censored graft survival was 90% while graft failure-free survival was 82%. Graft loss in some patients was linked to reduction of immunosuppression, some patients had problems with infections and one patient completely stopped his immunosuppressive medication.

Early AMR (onset during the first month post-transplant) occurred in 28% of XM positive patients, while another 10% were identified as late AMR; only one AMR occurred later than 6 months after transplantation. Most AMRs were not recurring. The majority of patients (92%) had satisfactory or good kidney function (≥30 ml/min/1.73m^2), and at 2 years the median estimated glomerular filtration rate was 61.5 ml/min/1.73m^2 (range: 22.4–106.7 ml/min/1.73m^2).

In summary, across all Phase II trials imlifidase treatment rapidly inactivated DSAs and converted positive XMs into negative. Rebound is expected in all cases, leading to AMR in some, but not all, patients. AMR incidence was consistent with expectations and aggressive treatment of AMRs is a key factor for successful long-term graft survival. At 6 months post-transplantation, 94% of patients had functioning grafts and were off dialysis. There were no graft losses due to IgG-mediated AMR. The safety profile of imlifidase treatment was consistent with that expected in a kidney transplantation population.

Imlifidase was granted a conditional marketing authorisation by the European Commission in August 2020 for "desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor."[36] This milestone launched a new era in kidney transplantation for selected patients who would previously have remained untreated.

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