Kidney allocation based on proven acceptable antigens results in superior graft survival in highly sensitized patients

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Highly sensitized renal transplant candidates accumulate on transplant waiting lists since they produce antibodies to many HLA antigens, which in this way become unacceptable. Organ allocation to these patients is usually based on avoiding transplantation of organs bearing these unacceptable antigens. In contrast, allocation through the Eurotransplant Acceptable Mismatch (AM) program is based on extension of the patient's own HLA type with so-called acceptable HLA antigens to which strictly no antibodies are formed, as shown by extensive laboratory testing. We questioned which type of allocation results in the best long-term graft survival. Therefore, we selected 58,727 cadaveric single renal transplant recipients transplanted within Eurotransplant between 1996 and 2015 and determined factors influencing graft survival for patients transplanted through the AM program. Next, we compared ten-year graft survival of patients with various sensitization grades who received a renal transplant through regular allocation to that of highly sensitized patients transplanted through the AM program. Unlike regular allocation, no effect for HLA mismatches existed for AM patients, while factors that did affect graft survival were similar to those of the general kidney transplant population. AM patients had significantly superior ten-year graft survival compared to highly sensitized patients transplanted on the basis of avoidance of unacceptable mismatches. Strikingly, graft survival of AM patients receiving a repeat transplant was similar to that of nonsensitized repeat transplant recipients. Thus, allocation of kidneys to highly sensitized patients based on proven acceptable antigens results in a significantly better graft survival compared to mere avoidance of unacceptable mismatches.

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Exposure to foreign human leucocyte antigen (HLA) molecules by pregnancy, blood transfusion, or transplantation can lead to sensitization in the form of alloantibodies.[1] HLA-specific antibodies are included in the immunological profile of a patient, and the transplantation-relevant antibody specificities are regarded as unacceptable antigens for the patient in question. Consequently, this results in the avoidance of organ offers that harbor ≥1 of these "unacceptable" antigens. Highly sensitized patients are difficult to transplant, and thus they accumulate on the transplant waiting list.[2] Several strategies are being followed to transplant highly sensitized patients, such as desensitization, paired donor exchange, as well as the avoidance of unacceptable mismatches by virtual crossmatching with priority for highly sensitized patients, such as in the new US kidney allocation system introduced by the Organ Procurement and Transplantation Network (OPTN).[3–5] While desensitization can create a window of opportunity to perform the transplant with a negative crossmatch, antibody-producing plasma cells remain present, which often leads to recurrence of the donor-specific antibodies that can contribute to (chronic) allograft rejection.[6–9] The probability of a highly sensitized patient receiving an organ through paired donor exchange is slim due to relatively small pools of donors.[2] Alternatively, allocation based on the avoidance of unacceptable mismatches with priority for highly sensitized patients could potentially be beneficial to highly sensitized patients by means of shorter waiting times,[5,10,11] but as we will show here, has limited benefit for long-term graft survival.

The Eurotransplant Acceptable Mismatch (AM) program was initiated more than 25 years ago to enhance transplantation of highly sensitized renal transplant candidates. Instead of avoiding transplantation of organs harboring unacceptable antigens, this program makes use of proven "acceptable" antigens, defined as antigens to which the patient has never formed antibodies, as proven by extensive laboratory tests.[12] Acceptable antigens are defined by the lack of antibody reactivity in complement-dependent cytotoxicity assays using target cells mismatched for a single HLA antigen, or single antigen-expressing cell lines. Additionally, since the early 2000s, B-cell epitope analysis using HLAMatchmaker (Rene Duquesnoy, Pittsburgh, PA) for HLA class I is used to aid in defining acceptable antigens. The increased chance of receiving an organ is achieved by allocation based on the

patient's own HLA with the addition of acceptable antigens. Through this addition of acceptable antigens to the patient's own HLA phenotype, and mandatory shipment of a compatible organ to AM patients, increased rates of transplantation of highly sensitized patients have been achieved.[13]

Here, we aimed to determine which factors influence long-term graft survival of AM patients. Furthermore, we compared long-term graft survival rates of patients transplanted on the basis of acceptable mismatches and those transplanted on the basis of avoidance of unacceptable mismatches to determine the true benefit of utilizing acceptable mismatches for allocation.

RESULTS

Factors influencing 10-year graft survival within the AM program

The study design is depicted in a flow diagram (Figure 1), whereas clinical characteristics of patients who received an organ through the AM program are listed in Supplementary Table S1. We performed univariate Cox regression analysis to determine which factors affected 10-year graft survival for AM patients (Table 1). Male donor sex was associated with a decreased risk of graft loss (hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.468 to 0.851; $P = 0.003$). Additionally, recipient age >50 years decreased (HR: 0.67; 95%

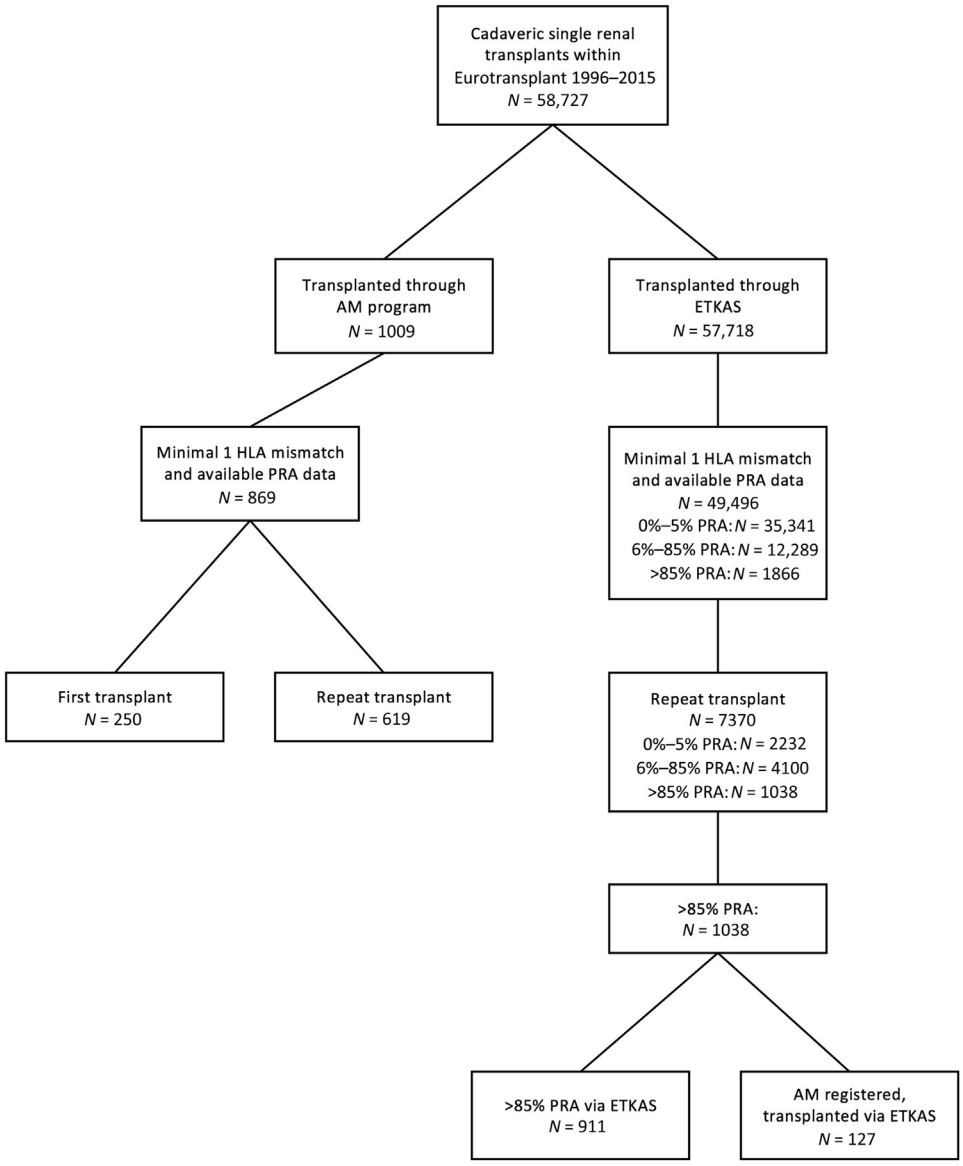

Figure 1 | Flow diagram of the study design. All cadaveric single renal transplants carried out in the Eurotransplant area between 1996 and 2015 were included in this study ($N = 58,727$). For death-censored graft survival comparison between patients transplanted through the Eurotransplant Kidney Allocation System (ETKAS) and the acceptable mismatch (AM) program, all patients receiving a renal transplant with a minimum of 1 HLA-A, HLA-B, or human leukocyte antigen (HLA)–DR broad antigen mismatch and available panel reactive antibody (PRA) data were selected ($n = 50,365$), from which 869 transplants were through the AM program and 49,496 through ETKAS.