

The Acceptable Mismatch Program as a Fast Tool for Highly Sensitized Patients Awaiting a Cadaveric Kidney Transplantation: Short Waiting Time and Excellent Graft Outcome

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There are many highly sensitized patients on the kidney waiting lists of organ exchange organizations because it is difficult to find a crossmatch negative cadaver kidney for these patients. Recently, several protocols have been developed to remove the donor-specific human leukocyte antigen (HLA) antibodies from the serum of these patients before transplantation. These approaches, including the use of intravenous immunoglobulins, plasmapheresis and immunoglobulins (plasmapheresis-cytomegalovirus-immunoglobulin), and immunoabsorption, seem to lead to a certain success rate, although the additional immunosuppression necessary to remove and control the production of donor-specific alloantibodies may have its impact on the short-term (infections) and long-term (incidence of cancer) immune surveillance. Furthermore, some of these therapies represent a considerable financial burden for patients and society. In the present report, we advocate selection of crossmatch negative donors on the basis of the Acceptable Mismatch Program, as the first and best option for highly sensitized patients to undergo transplantations. No additional immunosuppression is necessary, and graft survival in this group of "difficult" patients is identical to that of nonsensitized recipients. Because the nature of the HLA polymorphism does not allow all patients to profit from this approach, removal of circulating HLA antibodies can be considered as a rescue therapy for those patients for whom the Acceptable Mismatch Program does not give a solution.

Key Words: Highly sensitized patients, kidney transplantation, acceptable mismatches.

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Among all patients on the waiting list for cadaveric kidney transplantation, highly sensitized (HS) patients have the least chance to receive an offer (1). These patients have been sensitized by pregnancy, blood transfusion(s), and previous HLA-mismatched transplants. Patients with 85% or greater panel reactive antibodies (PRAs) are generally termed HS. The consequence of their high degree of sensitization is that most of the randomly performed crossmatches, as performed in many organ procurement organizations, will be positive, which is the main reason why there are so many HS patients on the waiting lists for cadaveric kidney transplantation (2).

Approximately 20 years ago, the problem of the increasing number of HS patients was noted, and several programs were established worldwide. In principle, there are two different approaches to help HS patients. The first approach

accepts the patients' high degree of sensitization and tries to find a crossmatch negative donor, and the second approach does not accept their sensitization and tries to remove the circulating alloantibodies. Recently, the second approach has received a lot of attention (3–7), but considering the additional immunosuppressive load (which is necessary for patients with donor-specific antibodies) we advocate that these approaches be used only if no crossmatch negative donors can be found for HS patients. In Eurotransplant (ET), the Acceptable Mismatch Program for finding a crossmatch negative donor for HS patients was initiated in 1985 (8, 9). Almost in parallel, the Save Our Souls (SOS) scheme was introduced in the United Kingdom (10, 11), and the Highly Immunized Trial started with a collaboration of centers in ET, Switzerland, the former Czechoslovakia, Poland, and Spain (12, 13). In the United States, a crossmatch tray program (Regional Organ Procurement, ROP) initiated by the Southeastern Organ Procurement organization was begun in 1994 to provide HS patients a better opportunity for an adequate kidney offer (14).

In contrast with the "trial-and-error" approach, followed by the Highly Immunized Trial, SOS, and ROP, in which sera of the patients are crossmatched with every available blood group-compatible cadaver organ donor and the majority of the crossmatches prove to be positive, the Acceptable Mismatch Program follows an alternative approach. On the basis of extensive laboratory studies, those HLA antigens are defined toward which the patient has never formed antibodies. These HLA antigens are considered to be acceptable as a mismatch in future kidney donors.

The Acceptable Mismatch Program makes use of the

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holes in the immune repertoire of the patients, which depends on the self-antigens and presumably also on those seen during the gestation (15) period, indicated by the non-inherited maternal antigens that are often included in the acceptable mismatch.

THE ACCEPTABLE MISMATCH PROGRAM

Patients in the ET-Kidney Allocation System (ET-KAS) (16) can also be included in the Acceptable Mismatch Program. Sera of at least two different bleeding dates must show that HLA antibody reactivity against the lymphocytes is 85% or more of the panel and that autoantibodies are not contributing to this panel reactivity. Both historical and current immunization of the patient is considered important (17). Acceptable mismatch can be defined by analysis of the HLA typing of panel donors with negative reactions in the screening (8). This is, however, only possible in patients in whom the PRA value is less than 100%. Alternatively, selection and crossmatching of blood donors with a single HLA mismatch to the patient’s phenotype can be performed (18). The formation of such patient-specific panels is possible because the ET reference laboratory can take advantage of a pool of more than 20,000 HLA-typed blood donors. Recently, additional enzyme-linked immunosorbent assay or flow cytometry-based commercially available kits have become available for the definition of acceptable mismatch. The use of the newly developed computer algorithm HLAMatchmaker (19) has been shown to facilitate the definition of additional acceptable mismatches. This algorithm is based on the concept that immunogenic epitopes are represented by amino acid triplets on those parts of the HLA molecule accessible to alloantibodies, and that those “self” triplets on the mismatched HLA-A or HLA-B molecules do not lead to alloimmune response. Serologic crossmatches with selected blood donor lymphocytes as targets were used to validate the theoretically assigned acceptable mismatch (Table 1). In the case of HLA-A- or HLA-B-mismatched donors with 0 mismatched triplets, all crossmatches were negative as predicted by the algorithm. By introduction of a single triplet mismatch, 2 of 133 crossmatches were positive. We conclude therefore that all 0-mismatched triplets can be seen as acceptable mismatches for the patients.

TABLE 1. Validation of the HLAMatchmaker19 by direct crossmatches

HLA-A mismatch		
	Expected negative	Observed negative
0 triplet	18	18
1 triplet	25	25
HLA-B mismatch		
	Expected negative	Observed negative
0 triplet	54	54
1 triplet	133	131

HLA, human leukocyte antigen.

SELECTION OF POTENTIAL ORGAN DONORS

A negative crossmatch with blood group-compatible cadaver organ donors is predicted on the basis of compatibility of the donor HLA-A, B, and DR antigens with the combination of the patient HLA-A, B, DR antigens and the acceptable mismatch. Minimal matching criteria of one HLA-B and one HLA-DR sharing or full HLA-DR compatibility are required. In case a donor with these requirements becomes available in one of the countries participating in ET, it is mandatory to ship the kidney to the recipient center, where the decisive crossmatch is performed using current and historical sera. In case of a negative crossmatch at the recipient center, the transplantation is performed. Obviously the logistic efforts for including patients in the Acceptable Mismatch Program are significant, whereas the workload to define the acceptable mismatch is higher than for non-HS patients.

WAITING TIME IN THE ACCEPTABLE MISMATCH PROGRAM

Earlier we showed that when patients entered the Acceptable Mismatch Program, they had a significantly higher chance to receive a cadaver organ than with the allocation system of the ET-KAS (20). The waiting list for the Acceptable Mismatch Program comprises 163 patients. In the period from January 1, 2002, to June 30, 2003, 129 patients entered the Acceptable Mismatch Program. In the same period of time, 68 patients underwent transplantation. Fifty-seven patients (mean waiting time 9.7 months, range 0–130 months) received the offer directly from the Acceptable Mismatch Program and 11 patients (mean waiting time 18.6 months, range 1–96 months) received the offer from the ET-KAS. The majority of the patients undergoing transplants arranged by the Acceptable Mismatch Program received the offer within the first 6 months after entering the program (Fig. 1). Thereafter and until the first 2 years, patients continue to receive offers but to a lesser extent, and finally a plateau is reached in which approximately 60% of the patients undergo transplantation. The main reason for this in the presence of a constant availability of cadaver organ donors is the immunogenetic profile of the patients. Comparing the HLA type of patients undergoing transplants arranged by the Acceptable Mis-

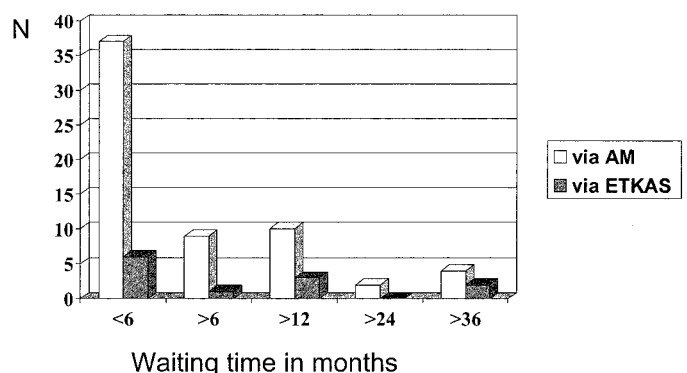


FIGURE 1. Allocation of cadaver kidneys to highly sensitized (HS) patients (January 1, 2002–June 30, 2003). AM: allocation through the Acceptable Mismatch Program (n=57). Kidney Allocation Aystem (KAS): allocation through the standard Eurotransplant (ET) system (n=11).

match Program and those who never received an offer, we observed that the latter group consisted of a significantly higher number of patients with unique HLA phenotypes, defined as HLA phenotypes not seen in 10,000 organ donors ($P < 0.002$; Table 2).

SURVIVAL OF THE TRANSPLANT

In addition to the short waiting time, the excellent graft survival of the transplants is a reason to use the Acceptable Mismatch Program as a first option for HS patients to undergo transplantation. The graft survival data of 112 patients who underwent transplants arranged by the Acceptable Mismatch Program in the period from 1995 to 2000 were compared with the other transplantation results within ET (Fig. 2). The graft survival of those in the Acceptable Mismatch Program (87% at 2 years) is identical to the group of the unsensitized patients in ET. Factors such as matching and historical versus current sensitization did not alter the results. These data confirm earlier observations and allow us to conclude that transplantation arranged by the Acceptable Mismatch Program offers the patient an excellent graft survival after cadaver kidney transplantation.

DISCUSSION AND FUTURE PERSPECTIVES

When no special programs are initiated, HS patients will accumulate on the waiting list of organ exchange organizations. In the present report, we show that the Acceptable Mismatch Program facilitates HS patients to undergo transplantation within an adequate time period with excellent graft survival. We observed that patients with unusual HLA phenotypes have the least chance to receive an offer. These patients have odd phenotypes because of their ethnic origin or rare antigen combinations when compared with the donor population. In addition, they tend to have antibodies toward frequently occurring HLA antigens. Consequently, the power of the Acceptable Mismatch Program diminishes after a period of 18 to 24 months. Patients will then accumulate on the list with a low or no chance to receive a crossmatch negative donor. Two possibilities are then available: to increase the donor pool and so increase the chances of patients for an adequate offer by international collaboration (21). If such collaboration is not possible, rescue therapies such as intravenous immunoglobulin (IVIg) treatment, plasmapheresis, or immune absorption should be considered. In conclusion, we propose a two-step treatment for HS patients: (1) A detailed definition of the HLA sensitization should be performed, and (2) the participation in an Acceptable Mismatch Program should be envisaged. In the meantime, the calcula-

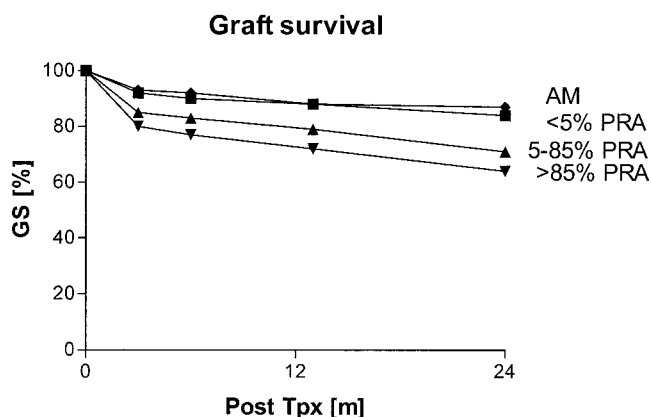


FIGURE 2. Comparison of graft survival between acceptably mismatched patients (n=112) and nonsensitized ($\leq 5\%$ panel reactive antibody [PRA]), sensitized (6%–84% PRA), and HS ($\geq 85\%$ PRA) recipients whose transplants were arranged through the ET-KAS (14,328). GS, graft survival.

tions of the chances of the patients to receive a crossmatch negative cadaver kidney should be performed (22). Removal of HLA antibodies by IVIg or plasmapheresis-cytomegalovirus-immunoglobulin or even immune absorption should be considered only in patients categorized with rare phenotypes. By this approach, an excellent graft survival and a short waiting time are guaranteed for a large proportion of these HS patients. Furthermore, the costs for transplantation and maintenance therapy will be significantly lower than in a situation in which all patients are considered for IVIg treatment.

In view of the long-term patient and graft survival, the reasons why patients are HS should be investigated. Decreasing the incidence of sensitization (e.g., filtering blood components and HLA matching in all kidney allocation procedures worldwide) will help in this direction.

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TABLE 2. Relevance of the organ donor HLA-A, B, DR phenotypes for acceptably mismatched patients

	Phenotype frequency	
	>1:10,000	<1:10,000
AM patients who underwent transplantation	23	1
AM patients who never received an offer	19	13
	$P=0.0018$	

AM, acceptably mismatched.

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