Update Article

IMPORTANCE OF DONOR SELECTION IN RENAL TRANSPLANTATION

Prof NK MEHRA*, Lt Col GS CHOPRA+

ABSTRACT

Renal transplantation has become a treatment of choice for patients with end stage renal disease. A successful transplant is the result of a combination of several factors acting synergistically, such as the degree of HLA compatibility between donor and the recipient, pretransplant blood transfusions, the recipient's state of immunoreactivity and sensitization, immunosuppressive therapy given in post operative period etc. Donor selection appears to be the most critical factor for the long term success of the organ graft. In this brief review, some of the important parameters of donor selection in renal transplantation are highlighted.

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KEY WORDS : Histocompatibility (HLA) matching; Cross match; Sensitization.

Introduction

Transplantation of solid organs is becoming increasingly successful. What was once an experimental and life saving emergency procedure, is now rapidly being transformed into a life enhancing and technologically advanced form of therapy. In any form of transplantation, donor selection is one of the most important and critical parameters which influences long term function of the allograft. In renal transplantation, donor kidneys are often obtained from cadaveric donors (CD) in most of the Western transplant centres through a very efficient multicentric collaborative programme. Large transplant organisations such as Eurotransplant Foundation (Holland), Scandiatransplant (Norway), UK Transplant Service (UK), United Network of Organ Sharing or UNOS (USA) exist in the developed world with a very high success rate of cadaver donor organ retrieval, sharing and transplant outcome. In India, almost all transplant centres utilize living donors who may be related (LRD) or unrelated (LURD) to the recipient. In the Armed Forces

renal transplantation has recently been started in a few centres like Delhi, Bombay and Pune with appreciable success. An important aspect of donor selection relates to HLA match grade between the donor and the recipient although other parameters such as age, sex, blood group status, pretransplant blood transfusions, crossmatch and sensitization of the patient also influence overall success of the graft to a variable degree.

HLA Matching

Cadaveric donor transplants are performed when the recipient has no family members as potential donors and the opportunity exists to receive a kidney from a recently deceased individual in whom brain death has been determined at the hospital. Possible contraindications in these cases are extra cranial malignancies, known case of hypertension, diabetes mellitus or any systemic infection. One of the major difficulties in selecting a cadaveric donor on the basis of matching, relates to the extraordinary degree of polymorphism that exists in the HLA system.

* Prof & Head, Histocompatibility and Immunogenetics Department, + Classified Specialist Pathology, presently on study leave at the Histocompatibility and Immunogenetics Department, All India Institute of Medical Sciences, New Delhi-110029.

Thus there is a little chance of getting a recipient who is HLA identical or more than 50% matched, unless a very large recipient pool is maintained and selection is done with the help of a computer. Survival of grafts in well matched groups i.e those sharing 3-4 class I antigens is about 10-35% superior as compared to the poorly matched group [1]. Matching for HLA class II antigen (DR antigens) is considered even more important [2] and thus donor recipient pairs that match for six antigens (two of locus A, two locus B and two HLA-DR) have been found to have much better long term graft survival than the zero-antigen matched group or those with one, two or more mismatches [3].

Data collected by the UNOS registry involving cadaver donor transplants show that donor recipient pairs mismatched for either class I or class II antigens have significantly lower short term graft survival rates as compared to well matched group [4]. Also HLA-A, B matching resulted in significant improvement in graft survival when analysed on long term basis. For example, in HLA well matched i.e six antigen matched transplants, one year graft survival rate of 88% and estimated half life of 17.3 years was observed as compared to 79% graft survival with half life of 7.8 years in zero antigen matched group. The half life is referred to as the period at which time atleast half of the grafts fail to function. The University of California Los Angeles (UCLA) transplant registry has completed data on more than 1,00,000 transplant. Graft survival was excellent in HLA identical siblings with half-life of 25 years as compared to 12 years with parental donors (one haplotype mismatch) and 7 years with two haplotype mismatch cadaver donors [5]. Introduction of cyclosporin A enhanced graft survival upto one year although the long term survival expressed as half life remained the same in this analysis. Six antigen sharing scheme in United States has produced transplants with better long term graft functions (87% at 1 yr) as compared to 81% in those with more antigen mismatches [3].

In LRD transplants, the donor is generally an immediate relative (siblings, parent or an offspring) in the family. HLA antigens being diploid in nature, each individual inherits two antigens of each of the HLA-A, -B and DR locus, one each from either parent. Thus a set of antigens on the same chromosome inherited *en bloc* from one parent is called a haplotype. Graft survival in HLA identical siblings has been found to be 100%, 92% and 77% at 1, 2 and 5 years post transplant period as compared to 95%, 71% and 61% respectively in the HLA non-identical group [6]. Recent AIIMS data has shown that four year graft survival for the grafts exchanged among more than 50% HLA matches between the donor and the recipient was 80% as compared to the 50% haplotype matched grafts in whom the corresponding figure was 67% [7].

Recently, with the advent of molecular typing of HLA gene products using polymerase chain reaction (PCR) and sequence specific oligonucleotide probes (SSOPs), it has become possible to further define HLA polymorphism at the DNA level [8,9]. The number of alleles identified by these techniques far outnumber those defined by conventional serological methods. Since sequences of most HLA class II alleles are known, it has become easier to type them by molecular techniques. Such procedures are increasingly being employed for cadaver donor transplant situations since matching can be done for allele subtype differing at even a single amino acid substitution level and exact genotype can be defined in most cases. Molecular techniques are therefore beneficial for optimal HLA class I and particularly class II antigen matching and are definitely more sensitive, accurate and rapid methods of tissue typing in organ transplantation [10-12].

Opelz and coworkers [13] have reported that upto 25% of serological HLA-DR typings may be incorrect when compared with the more accurate DNA based methods. The one year transplant success rate for DNA matched HLA-A, B, DR grafts was 87% compared with 69% for mismatched grafts ($p < 0.02$). They

suggested that many transplants that were previously thought to be HLA matched are in fact mismatched and this may account for previously unexplained graft failures.

Currently, several DNA typing methods have become available which include PCR-SSOP, PCR-SSP, PCR-RFLP to typing strategies on microtest plates or reverse dot blot procedures. The complete procedure can be done in a matter of hours (3 hours or so) involving multiple samples and can be adapted to clinical practice by fully-automated pipetting using a robotic workstation. The impact of molecular matching in clinical transplantation is enormous. The results of several transplants using this method of matching indicate that kidneys exchanged on a 11-molecular residue match grade have an 84% overall 1-year survival for first cadaver grafts [14]. Moreover the 10-year projection has increased from 38% using serological methods to 52% using molecular matching i.e one and a half times more kidneys would be functioning 10 years later.

Use of epitope matching rather than single allele matching has recently been suggested in UCLA transplant programme [15]. However, the ultimate matching approach will probably be based on nucleotide sequences.

Effects of age and Sex

UCLA International Transplant Registry data on more than 100000 cadaver donor renal transplant performed in several centres during the last 10-15 years has indicated that donor age plays a significant role both in patient as well as graft survival [16,17]. Kidneys transplanted from younger donors (< 40 yrs) generally have markedly superior survival rates as compared to those obtained from older donors (> 40 yrs of age) and higher graft failure has been reported when kidney donor is more than 60 years of age [18]. It has also been argued that younger recipients with less than 30 yrs of age generally have a poorer 'long term' graft survival as compared to older recipients [19] possibly because of the fact that younger recipients are immunologically higher responders than older patients.

According to the UNOS data, kidneys both from very young (< 9 yrs) as well as older (> 55 yrs) donors failed more often than those obtained from middle aged (17-32 yr) group [4]. No significant differences were observed in graft survival when male donors were used (94%) as compared to female donors (92%).

Blood group Status

A,B,O blood group system is present not only on erythrocytes, but also on the vascular endothelium of the graft [2], making it necessary that transplants are performed only between A,B,O compatible pairs. Role of plasmapheresis and immunoadsorption for reducing anti-IgM antibodies and to overcome ABO blood group incompatibility barrier has shown encouraging results [20] although the long term effects of these procedures are still unknown. Recently, Bryan et al [21] observed that donors with A2 blood group can successfully donate kidney to Non A blood group recipients provided that the patients have low sensitization. However, further trials are necessary before such a data is utilized in general transplantation.

Sensitization

Sensitization or formation of preformed lymphocytotoxic antibodies is amongst the more difficult problems encountered in donor selection in renal transplantation. Patients with alloantibodies must have had contact with foreign HLA antigens in one form or another. It is now well established that previously rejected allografts, pregnancies, pre-transplant blood transfusions or infections are dominant causes of sensitization [22-23]. Recipients with reactivity against a panel of lymphocytes from random individuals are categorized as positive for panel reactive antibodies (PRA), and face delays for transplantation even after a suitable donor has been found. It has been observed that patients with greater than 50% PRA activity are highly sensitized and show significantly lower graft survival rates than the non-sensitized (<10% PRA) group or those that are moderately sensitized (11-50% PRA) [24,25]. Experience at

the AIIMS hospital indicates that patients with > 10% PRA developed significantly ($p < 0.05$) more rejection episodes than those with <10% PRA. Also, highly sensitized patients with PRA above 50% are significantly more likely to develop a positive lymphocytotoxic cross match against donor lymphocytes [26]. Thus PRA test can be used to predict which patient is likely to develop donor reactive antibodies and this information can be of great help in cadaver donor transplantation where donor is available at a very short notice. Regular monitoring of PRA activity following transplantation has been found to be a reliable indicator of the sensitization status of the patient. Experience at AIIMS shows that high post transplant PRA levels are associated with more frequent rejection episodes and irreversible rejection in extreme cases [26].

Several strategies have been developed to decrease the chance of sensitization. These include elimination of unnecessary blood transfusions [27], detection of antibody specificity ie IgG or IgM [28], ensuring good HLA compatibility [29], and removal of preformed allo-antibodies by cyclophosphamide treatment in combination with plasma exchange [30].

Cross Matching

Cross match between the serum of the recipient and lymphocytes of the donor remains the most crucial aspect of donor selection for renal transplantation. It is used to determine the presence of any preformed antibodies to donor antigens. A conventional cross match is performed by the microlymphocytotoxicity test [31] by using patient's most recent serum and donor's peripheral blood lymphocytes (PBL) or separated T and B lymphocytes. The test is usually done at different temperatures (4°C, 37°C and room temperature) which provides better definition of the specificity of antibodies present in the recipient serum. The serum is also checked for autoantibody and whether or not the antibody is of IgM nature by absorbing the recipient serum with dithiothreitol (DTT).

The cross match procedure is always repeated one day prior to transplantation so as to detect any new sensitization due to blood transfusions. Recently, flowcytometry has been employed for cross matching of renal and other organ transplant patients. It is a more sensitive and accurate method than the conventional NIH microlymphocytotoxicity technique and can be used to detect sub-threshold levels of antibodies and those directed to various cell types. The procedure is particularly of value in retransplant and highly sensitized recipients. Piazza *et al* [32] from their study of 125 patients concluded that flowcytometric cross match is a useful and fundamental test in donor recipient selection since it allows identification of patients at potential immunologic risk. They also advised monitoring and detection of post transplant donor specific antibodies by flowcytometry. According to these investigators, regular post transplant flowcytometric cross match provides useful information on the degree of sensitization which may help the clinician in instituting an effective immunosuppressive therapy. These findings have recently been confirmed by others [33]. Studies carried out by us at the AIIMS and Army Hospital, New Delhi have indicated the value of the post-transplant flowcytometric cross match in the detection of early donor specific graft rejection and differentiating it from cyclosporin A induced nephrotoxicity [34].

It is generally agreed that a positive cross match against T-cells is a definite contraindication for a renal transplantation. However, transplants made in the presence of B cold or T and B cold antibodies (autoantibodies) are not rejected and may even show enhancement while presence of T and B warm antibodies (at 37°C) may not be good for the graft [35]. The recognition of these different antibodies have allowed a number of highly sensitized patients to be transplanted, which otherwise would have remained untransplanted. Also there is now a consensus that a patient with a historical positive cross match but a current serum negative results can be transplanted reasonably safely.

Donors in Retransplantation

Success rate for renal retransplantation have consistently lagged behind those of first transplants. Sensitization associated with the loss of a transplanted kidney is generally regarded as a major obstacle to retransplantation. Recent UCLA data has shown that 70% of the retransplanted patients had measurable panel reactive antibodies as against 34% of the single transplanted cases. Also, patients with PRA levels of more than 10% have significantly lower graft survival than the less sensitized group [36]. It is now generally agreed that patient requiring a second transplant should have a better matched donor as it is associated with decreased degree of sensitization and thus possibilities of enhanced graft survival [1]. The second donor should preferably not carry the same mismatched HLA antigen as of the previous donor [37]. This avoids the boosting effect of sensitization.

Conclusion

From the above, it is apparent that histocompatibility matching unquestionably offers the best approach to prevention of chronic rejection and significantly influences the long term success of a renal transplant. The only cure to combat chronic rejection might as well be termed as 'preventive' that is the graft should come from a well matched donor. It will also mean that less immunosuppression may be necessary in the well matched donor-recipient pairs resulting in fewer post-transplant complications.

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