

Strategies to expand the living donor pool for kidney transplantation

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1. ABSTRACT

Structural shortage of deceased donor kidneys for transplantation has resulted in the expansion of living donation programs. A number of possibilities are now being explored, since it became clear that donors do not need to be genetically related to their recipients. Apart from classical direct donation we now conduct paired exchange, list exchange, altruistic donation and domino paired exchange programs. Other alternative programs are desensitization and transplantation across the blood type barrier. The purpose of this article is to give a general view of all optimizing living donation programs by reviewing the literature. First we describe logistic solutions, thereafter the more intensive medical treatments. We observed a wide variation in clinical experiences with living donation dependent on local jurisdiction, culture and customs. Professionals disagree on various ethical issues inherent to alternative programs. In our opinion logistic solutions like paired exchange, list exchange and altruistic donation programs are to be preferred over the more medical demanding programs e.g. desensitization and transplantation across the blood type barrier.

2. BACKGROUND

Deceased donor organ shortage has become the major limitation in our attempts to expand kidney transplant programs. In the eighties of the last century the wait time for a kidney transplant was approximately one year. Since that time the success rate of a organ transplantation has significantly improved which attracted large numbers of transplant candidates. As the number of deceased organ donors did not increase, the wait time on the list steadily grew and at the moment patients in most Western countries face wait times up to 5 years before a deceased donor kidney is offered. Unfortunately an increasing proportion of them will never be transplanted because their clinical situation deteriorates to such an extent that they are delisted or die on the wait list. For the Netherlands we estimate that this proportion is approximately 30%. A strategy to expand the kidney donor pool includes the use of non heart beating (NHB) donors. Educational programs in the Netherlands have resulted in a huge increase in the number of kidney transplants derived from NHB donors from 77/387 (19.9%) in the year 2000 to 168/384 (43.7%) in 2006 but this has not led to expansion

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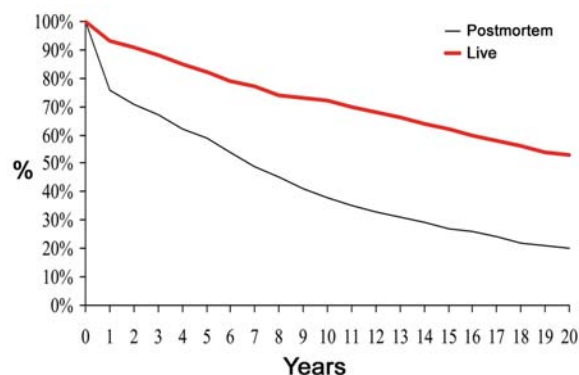


Figure 1. Unadjusted graft survive of 13.000 deceased donors and 2500 living donor kidney transplants performed in the Netherlands between 1966 – 2006.

of the deceased kidney donor pool. Possibly substitution from heart beating to non heart beating donation procedures took place, resulting from pressure on the facilities of intensive care units. In the Netherlands, it has been suggested that the main reason for our failure to increase the number of deceased organ donors is the lack of donor detection. This is certainly not the case; both in 2005 and in 2006 almost all potential donors in the Netherlands (96%) were recognized as such and for the vast majority (86%) our national donor registry was consulted. The problem is not donor detection but the high refusal rate by the next of kin, which is inherent to our legal system. Our organ donation act dictates an opt-in system, and therefore all adult citizen are asked to register their consent for the use of their organ for transplantation purpose after death. In the Netherlands approximately 25% of the adults are now registered as potential donors, 15% have explicitly refused and thus for 60% it remains unknown. Especially in case of potential donors of the latter category high refusal rates up to 70% haven been found. Apparently next of kin argue that while the possibility was given to everybody to register as donor, their relative did not do so, therefore they are unaware of consent and thus reluctant to give permission for donation. We feel that an opt-out organ donation system would be very much helpful to expand the deceased kidney donor pool. However, we are aware that even if all potential deceased donors became actual donors, there still would be a shortage of donor kidneys. Therefore the use of kidneys from living donors is an obvious way to go. These transplants result in a superior unadjusted graft survival compared to deceased donor kidneys. It has been calculated that the difference in 10 years survival between living and deceased donor kidney transplantation is 34 % (Figure 1). Thus not only in terms of quantity, but also because of quality, living kidney donation is a good option. Moreover, due to the use of minimally invasive surgical techniques the morbidity for the living donor is acceptable, the mortality risk of donor nephrectomy is low, and long term survival of kidney donors is unaffected. The present review describes the strategies that can be followed to expand the living kidney donor pool. The first is the shift from the genetically related donor to the unrelated donor which already resulted in a large increase in kidney transplantations especially by partner donation. The second strategy includes the attempts

to circumvent or to overcome cross match- and blood type barriers that normally would have precluded donation. Both logistic solutions such as the various exchange programs and the medical interventions as desensitization programs of anti-HLA antibodies and isoagglutinins will be described.

3. OPTIMIZING PROGRAMS

3.1. Living unrelated kidney donation: shifting donor profiles

Transplantation of kidneys derived from living genetically related donors has been performed since 26 October 1954, when an identical twin transplant was successfully performed in Boston. In the years that followed, efforts to enable non-twin transplants unfortunately failed because effective immunosuppression was not yet available. It took until the early sixties after the discovery of azathioprine that also living non-twin transplants (allografts) became possible with an estimated 80% one year graft survival (1). This relative inadequacy of azathioprine based immunosuppression made HLA matching between donor and recipient desirable if not necessary. This explains why a strong preference developed for living genetically related donors. With the introduction of more effective immunosuppressive regimens based on calcinurin inhibitors, it appeared that HLA matching became less important and good results could also be obtained in poorly matched donor-recipient combinations. Thus gradually the pre-requisite for living kidney donors to be genetically related disappeared. Subsequently it became clear that the graft survival of these poorly-matched transplants from living genetically unrelated donors was excellent (2). As a result, increasing numbers of these transplantations were performed with kidneys derived from genetically unrelated, but emotionally related donors. Especially spouses gained a lot by donating: by helping their life-companions they could consequently lead a healthier life together. Therefore it is not surprising that spouses and partners for a large part have been responsible for the significant increase in living donation numbers over the last decade. Living genetically unrelated donors accounted in 2006 for 2365/6435 (37%) of living donation in the U.S.A., 386/906 (43%) in the Eurotransplant area, 130/274 (47%) in the Netherlands and 43/75 (57%) in Rotterdam. In the USA 33% (785/2365) of the living unrelated donors were spouses, 72% (279/386) in the Eurotransplant area, 52% (68/130) in the Netherlands and 37% (16/43) in Rotterdam (Figure 2). The figure also shows the proportional contribution of living donation for the total kidney transplant programs.

3.2. Living donor kidney exchange program

3.2.1. History

Unfortunately not all willing donors can donate directly, due to a positive cross match or an ABO blood type incompatibility. In these cases, exchanging donors could be a solution (Figure 3). A living donor kidney exchange program was originally described by Felix Rapaport in 1986 (3). He proposed anonymity between donor-recipient pairs and that the operation had to be carried out in two different centers at the same time. After

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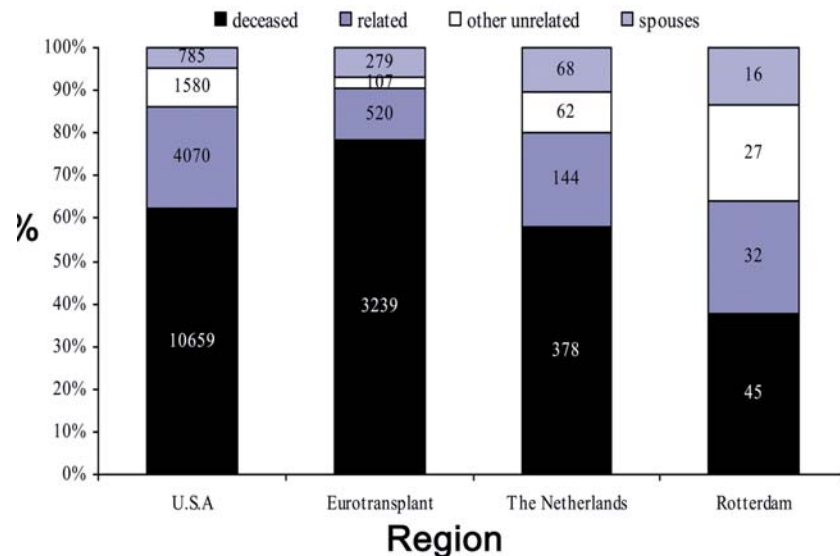


Figure 2. Donor source for kidney transplantations in 2006.

the donation-procedures the kidneys were supposed to be transported to the acceptor center. Five years later in 1991 the first real living donor kidney exchange procedure between two families was performed in South-Korea (4). Because of cultural and religious reasons the organ exchange between living donors is easier to accept than the concept of brain death and cadaveric donation. Therefore the majority of kidney transplants are dependent on living related or unrelated donors. In 1995 Park introduced a living donor kidney exchange program with no limit in combinations (up to six pairs). His team performed 101 living donor kidney exchange procedures from 1995 to 2003 (11 per year). Several centers in the USA started in 2000 and 2001 living donor kidney exchange programs. Living donor exchanges is legal in the USA because there are no valuable considerations under the National Organ Transplant Act of 1984. There is no strict anonymity between the donor-recipient pairs. It is possible to meet or contact the other couple some days after the transplantation but all couples must agree on this. From 2000 until 2006 85 paired donation procedures were performed resulting in 170 kidney transplants (5). Most of these procedures took place within the same center. Alternative options to expand the living donor kidney exchanges could be to maximize the size of exchanges. Saidman *et al* did a simulation with 45 patients data in two- and three-way exchanges. (6). On theoretical grounds we found a possibility in our Dutch program to perform a 17-way exchange. Obviously this is not the practical way to go for logistic reasons. To optimize kidney exchange programs a permanent regional or national collaboration is a necessity. One of the greatest obstacles to the implementation of such a program is the need for the donor to travel to the recipient center which might be a logistic problem for a vast country. Therefore recently the old proposal of Rapaport to ship the donor kidneys has been revitalized (7). Other initiations to implement living donor kidney exchange programs took place in Canada, United Kingdom and The Netherlands. In Canada they performed the first living donor kidney exchange procedure in November 2005. There is a great

deal of support and excitement for a national exchange program across the various transplant programs in Canada, but a lot of logistic barriers are still to overcome. The United Kingdom changed their law in September 2006. The new Human Tissue Act and the Human Tissue Act (Scotland) will allow non-directed donations. UK Transplant is exploring how best to facilitate these new exchange program. In the Netherlands a living donor kidney exchange program started in 2004 in which all Dutch transplant centers cooperated (8). Conditions for such a program include that an independent organization, the Dutch Transplant Foundation, is responsible for the allocation. Our allocation criteria are based on the maximum number of transplants possible within one match run; blood type, first identical than compatible; match-probability, wait time and donor age. The match-probability is based on the prevalence of both blood types and HLA antigens in the actual living donor exchange pool. One central laboratory for histocompatibility performs all the cross matches between the recipients and their newly matched donors. Medical and logistic issues are described in a national protocol.

3.2.2. Dutch experience

From January 2004 to April 2007, a total of 206 donor-recipient combinations were enrolled in the program which is now the largest in the world. In 100 cases the reason for enrolling was a positive cross match and in 106 cases ABO blood type incompatibility. The recipients had a median wait time of 17 months on the cadaveric waitlist (range 0-268 months). The median age of the patients was 52 year (range 17-73 year). The oldest donor in this program was 78 years, the youngest 27 years (median 53). Table 1 shows the blood type distribution of donor and recipients. Median PRA in the positive cross match group was 42 % (0-100%) and 2% (0-100%) in the ABO blood type incompatible group (Figure 4). Every three months participants can be registered for a match procedure. From January 2004 until April 2007 fourteen match procedures were performed. The median input of new donor-recipient

Table 1. Blood type distribution of donors and recipients

Donor ¹	Patient ¹				donor ²	Patient ²			
	AB	A	B	O		AB	A	B	O
AB	-	3	1	2	AB	-	-	-	-
A	-	-	16	64	A	3	32	-	-
B	-	12	-	8	B	-	-	2	-
O	-	-	-	-	O	-	17	9	37

¹Blood type incompatible donor-recipient pairs, ²Positive cross match donor-recipient pairs

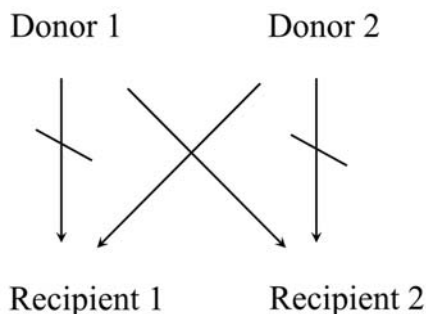


Figure 3. Living donor kidney exchange

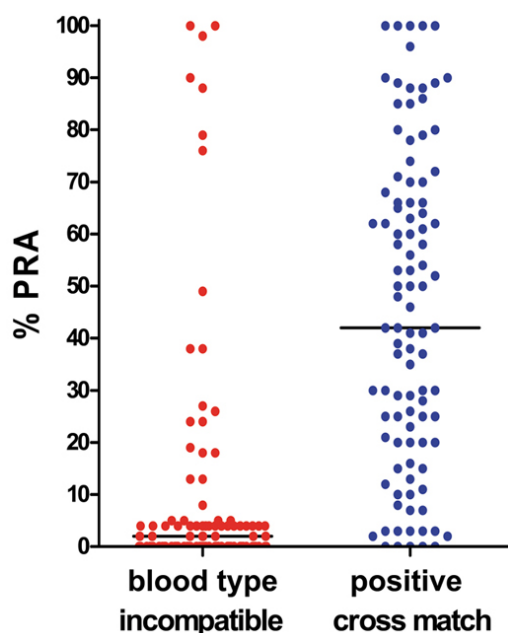


Figure 4. Peak PRA % in blood type incompatible and positive cross match recipients (n = 206).

pairs was 14 (range 7 – 21 pairs) and the median number of couples participating in a match procedure was 43 (range 16 -56 pairs). On the basis of allocation criteria the computer constructed 109 ABO compatible cross match negative new donor-recipient pairs. These 109 pairs were derived from 71 positive cross match pairs and 38 ABO blood type incompatible pairs. In the positive cross match group there was no difference in success rate of pairs with O recipients (26/37, 70%) and pairs with non-O recipients (45/63, 71%). However, in the ABO blood type incompatible group the success rate of O recipients (15/74,

20%) was significantly ($p < 0.0001$) lower than for non-O recipients (23/32, 72%). After 3 match runs chances for success became small (Figure 5). The overall success rate for blood type O recipients (41/111, 37%) was significantly lower than that for blood type non-O recipients (68/95, 72%). Of the 97 couples for which no match was found, 46 are still in the program while 51 others definitely left: 15 were delisted for medical reasons, 24 received a deceased donor kidney, while for 12 others an alternative living kidney donor was found. In total after 42 months the Dutch living donor kidney exchange program resulted in a 53 % (109/206) success rate. For the unlucky not-matched pairs other programs are necessary.

3.3. Living donor list exchange

To expand the living donor pool, living donor list exchange can be another logistic solution. The donor of an incompatible living donation-couple donates a kidney to a candidate on the wait list while in return the acceptor of that incompatible couple receives the first available kidney from the deceased donor pool (Figure 6). In 1998 and 2000 Ross and Woodle described this indirect paired list exchange program (9). They discussed the risks and benefits of these exchanges. The patient of the incompatible donor-recipient pair trades the minimum wait time for a lower graft survival. The candidate on the cadaveric wait list is also satisfied, he receives a living kidney instead of a deceased donor kidney. For the living donor, the medical treatment is the same, thus he is happy to indirectly help the patient. The consequences and the disadvantage of living donor list exchange is the growing wait time for blood type O recipients without a willing living donor, as most participating couples will consist at a blood type O recipient and a blood type A, B or AB donor. This implies that priority is given to this O recipient over other O recipients who are higher on the deceased donor wait list and have waited longer. Delmonico *et al* performed the first 17 list-exchange transplants (10). He reported the disadvantage of the O recipients, but he argued that this harm would be transient. Zenios and Ross disagree; they think that this effect persists over time (11). Moreover Veatch stated that an allocation system should benefit those who are worst off, which is not the case in a living donor list exchange program (12). Due to all these arguments the number of living donor list exchanges is not overwhelming in the USA. In eleven years (1996-2006) 71 such transplants were performed. In May 2006 the Dutch Transplant Foundation requested a pilot study to start a living donor list exchange program. However, the authorities have excluded the possibility of living donor list exchange in the Netherlands on the basis of the Dutch Organ Donation Act. It is argued that, although a living

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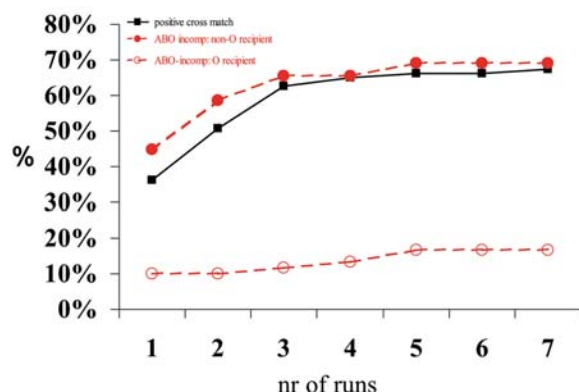


Figure 5. The chances for a donor-recipient pair to find a match in relation to the number of allocation procedures in which they participated. Nr: Number of runs

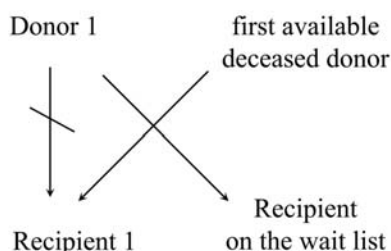


Figure 6. Living donor list exchange.

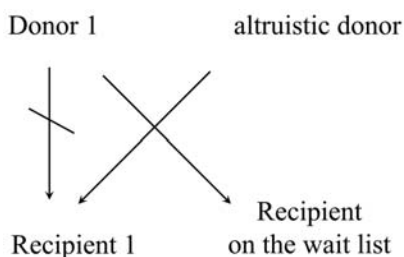


Figure 7. Domino paired kidney donation.

donor list exchange program will result in more transplants, equal access to health care is not guaranteed anymore and therefore the program does not fulfill the fundamental principles of Dutch law.

3.4. Altruistic donor program / Domino paired exchange program

Another major challenge to increase the number of living donors are the so-called 'Samaritan' donors or altruistic nondirected living donors'. Starting in the USA transplant centers have been approached by individuals offering to donate a kidney to patients unknown to them. Already in 1971 Sadler was the first who described a number of Samaritan donors (13). However, in the seventies and eighties these offers were not accepted because the opinion was that these donors would be mentally instable (14). Thereafter, the first transplantation with an altruistic donor was performed in 1998 in the USA. The number of this type of kidney transplantation has steadily increased from 3 transplants in 1998 to 71

transplants in 2006. Several authors reported about ethical issues including the evaluation of the donor, the allocation and non-directed or directed donation. Matas and colleagues recommended that the evaluation of altruistic donors should include a psychosocial evaluation to rule out underlying psychiatric disorders and to ensure decisional capacity (15). They defended that no stricter medical criteria for nondirected donors were needed compared to emotionally-related living donors. Furthermore, the Minnesota team stated that they used the UNOS algorithm, but limited the altruistic donations to recipients listed at their own center. In respect to altruistic donation a third issue is directed donation. Should these donors be allowed to select their recipient? Spital *et al* collected data of surveys regarding the public's attitude toward directed altruistic donation. He concluded that anonymous donors should not be allowed to donate directly to a particular subgroup (16). However, Hilhorst *et al* disagreed and argued that preferences of altruistic donors for a certain patient or patient group should not be classified as a restriction or discrimination of others (17). The specific wishes of donors may flow from very basic feelings and particular loyalties. The authors suggested that the fear for racial and religious discrimination that could be distilled from Spital's survey, would not have appeared if the topic had been presented in a more positive, less biased way. Another option to expand this type of donation is domino paired kidney donation, in which an altruistic donor donates to the recipient of an incompatible donor-recipient pair while the donor of this pair gives in turn a kidney to the next compatible patient on the wait list (Figure 7). So one nondirected donor can double the number of transplants (18). Another option to help more transplant candidates is the idea of chain exchanges from the New England group in which list exchanges and non directed donations can enter a chain of transplants that not even have to be performed at the same time (19). We advised to integrate all these options in a national exchange program under supervision of an independent allocation authority and have performed 9 domino-paired donations with unsuccessful paired exchange pairs resulting in 18 kidney transplantations (20). Other transplant centers from Europe seem more conservative about altruistic donation, although one surgeon in Germany reported his own experiences as an altruistic donor (21).

3.5. Alternative options for incompatible donor-recipient combinations

If logistic solutions such as living donor kidney exchange, living donor list exchange or domino paired exchange are not available for a recipient whose only living donor is incompatible, more costly and risky protocols have been developed over the last years. Desensitization protocols could be a solution for donor-recipient pairs who have a positive cross match. Also for an ABO incompatible living donor-recipient pair several protocols have been developed with different pre-operative and post-operative interventions.

3.5.1. Desensitization program

A direct donation of a living donor is not possible due to a positive CDC (complement dependent

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cytotoxicity) cross match, which indicates the presence of preformed cytotoxic IgG antibodies in the serum against human leukocyte antigens of the living donor. Sensitization to HLA antigens can occur by three mechanisms: pregnancy, transfusion of blood products containing leukocytes or platelets, and organ transplantations. Two desensitization therapies are showing great promises; High-dose IVIG protocols and/or plasmapheresis protocols, in association with the use of newer immunosuppressive drugs. These approaches to remove anti-HLA-antibodies are not novel interventions, but their recent success has certainly contributed to a better understanding and diagnosis of acute antibody-mediated rejection.

3.5.1.1. High-dose IVIG protocol

This involves intravenous administration of high-dose Immunoglobulins (IVIG) to down regulate alloresponses. IVIG can remove and reduce the synthesis of allo-antibodies. Several studies have been published, which diverged in timing of the IVIG infusion, the administered dose, and the additional immunosuppressive therapy. Two studies with high-dose IgG protocols were reported by Jordan *et al*, one study with 42 highly sensitized patients who were treated with 1-4 doses of IgG and underwent a kidney transplant (22). The 2-year allograft survival rate was 89%. 31% of the patients had an acute rejection which resulted in three graft losses. The second study of Jordan was a randomized, double-blinded controlled trial of IgG versus placebo in highly sensitized patients with a minimum PRA of 50% (23). IgG was given monthly for 4 months at 2 g/kg per dose. 35% of the IgG group received kidney transplantations versus 17% of the placebo group. The 2-year graft survival was 80% in the IgG group and 75% in the placebo group. In the most recent publication of Jordan he evaluated 77 highly sensitized patients who had positive cross match tests with their potential donors in the IVIG-PRA test system (24). Desensitization was in 97% of the patients successful and, due to various reasons, 87% underwent kidney transplantation. Thus, only 2/77 (2.6%) failed to respond to IVIG sufficiently to allow transplantation to be considered. The incidence of allograft rejection was 28%. The 3-year graft survival rate was 87.1%. Five grafts were lost to rejection. While each protocol has allowed successful transplantation, comparisons have been difficult because of significant differences in the patients treated, the assays used to define the levels of donor specific antibodies and the outcomes studied. It should be emphasized that long-term outcomes are not yet available and it is an expensive therapy. Advantages are that this protocol is easy to administer, no immunosuppression is used and this therapy is relatively non-toxic.

3.5.1.2. Plasmapheresis-based protocols

This therapy is used to remove anti-HLA antibodies in combination with low doses of IgG. Plasmapheresis is given three times per week immediately followed by a low dose of IgG. Twice daily patients were treated with tacrolimus and MMF. This scheme is continued until the cross match is negative with the living donor. At that moment transplantation takes place within 24 h. In the Hopkins protocol Rituximab is given the day

before transplantation only for patients who have had previous transplants, previous early graft losses and multiple anti-HLA antibodies specificities (25). The group of Gloor has a more aggressive protocol wherein patients also underwent splenectomy and all received rituximab (26). In general the disadvantages of plasmapheresis protocols are their associated morbidity; they have not been evaluated in randomized-controlled trials, while they are expensive and labor intensive.

3.5.2. Transplantation across the blood type barriers

In the sixties and seventies, sporadic reports of ABO incompatible kidney transplantations demonstrated poor results, and therefore the procedure was largely abandoned. In Japan where patients are largely dependent on living donation for cultural reasons, several groups made continuous efforts to perform transplantation across the blood type barriers (27,28). Most ABO –incompatible kidney donors have been A1 or B, the less antigenic A2 blood type is uncommon in Japan. Pre-operative anti-A/B antibody removal and splenectomy were routinely performed combined with triple or quadruple immunosuppression. The overall graft survival rate at 1, 3, 5 and 10 year after transplantation was 86, 82, 74 and 53% respectively. In the late 1990s, transplant centers in Europe and the USA became interested in ABO incompatible kidney transplantation programs. In Sweden Tyden *et al* designed a protocol without splenectomy, based on antigen-specific immunoadsorption, rituximab and a conventional triple-drug immunosuppressive protocol (29). They used specific absorption columns coated with blood type A or B. The first ABO incompatible transplantation with this new protocol was performed in Stockholm in 2001. Since 2002 they used the protocol as a routine procedure. Thereafter 20 other European centers, particularly in Germany, United Kingdom, The Netherlands, Switzerland, Greece, France and Spain has implemented this protocol. Tyden *et al* reported in 2007 the results of 60 ABO incompatible kidney transplantations performed in Sweden and Germany in the period between 2002 and 2006 (30). The graft survival was very impressive 97%. In the United States, the most common protocol has used blood subgroup A2 donors for B or O recipients. When the donor is A2 and the anti-A2 titer is low at baseline, most centers would not perform antibody reduction protocols preoperatively but would monitor closely for antibody-mediated rejection post transplant. When the anti-A blood group titer is high with an A2 donor, most centers would advocate pretransplant antibody reduction, with plasmapheresis being the most commonly used method. Gloor *et al* reported a study about the need for splenectomy versus intensive posttransplant antidonor blood group antibody monitoring (31).

4. PERSPECTIVES

For health care professionals living kidney donation have important advantages over cadaveric donation. So they have to promote the many options of living kidney donation programs, in an attempt to make more kidneys of high quality available for transplantation. In that respect logistic issues should be arranged for the paired exchange, list exchange and domino paired

exchange programs. It is important to devise uniform protocols for the evaluation of the (altruistic) donor. Transplant centers may opt for an independent organization to supervise and discuss the allocation criteria of these programs. Although logistic issues are important, we also have to pay attention to ethical dilemmas. Will patients and their relatives accept all living kidney donation programs? First of all, patients and their relatives must be well-informed about all relevant facts with respect to the various treatment modalities. Health care professionals have the responsibility to explain the benefits but also the risks of the diverse programs. They should also thoroughly explain alternatives. Only then it is possible for the patient to make a well balanced decision. Another issue in this respect is the environment of the patient. Every single relative and relation feel a certain pressure to be a potential living donor. Family members, partners, good friends, neighbours and colleague can act all as a living donor. So the question arises, 'how voluntary are these donors?' Each relationship between a patient and a potential donor has its own unique characteristics. It is very difficult to find out where the interest of one person ends and where the interest of the other begins, especially when spouses are concerned. If the partner donates his/her kidney, he/she regains a healthier partner and they can have good opportunities for a better life together. With all the optimizing and alternative programs the pressure on relatives of the patients to donate will become higher. They have no medical excuses anymore. When direct donation is not possible, exchange programs or alternative programs can bring a solution. So incompatibility between donor and recipient does not spell the end of all hope. However, they should feel free of coercion. This ethical obstacle may not be applied to altruistic donors. They make their own, autonomous decision and have their personal reasons for their choice to become an altruistic donor. But nevertheless, is promoting of an altruistic program the responsibility of each individual transplant centre or the duty of the government? The same question arises when living unrelated donations is not allowed by law. The transplant community and the government have to accept their responsibility to explore the possibilities of a legal change. An excellent illustration is United Kingdom, their law changed in September 2006. A living donor kidney exchange and an altruistic donor program became realistic options for them. Professionals should also discuss financial issues with health care institutions to make possible the expensive, alternative programs like desensitization and transplantation across the blood type barrier. Another financial topic to be considered is a regulated system of paid living kidney donation with a fixed price with the aim to fairly reimburse the donor thereby undermining the black market (32). Obviously there should not be a role for illegal brokers in this concept. Several authors have discussed the issue of the kidney as commodity, correctness of financial motivations, and the fear for exploitation. Payment for organs is illegal in most countries, but transplant communities should continue to discuss the possibility of a regulated organ market as long as the illegal systems are still harm the poor and underdeveloped.

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Key Words: Living Kidney Donation, Kidney Exchange Programs, Altruistic Donors, Desensitization Programs, Transplantation Across The Blood Type Barrier, Review

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