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Strategies to increase the donor pool and access to kidney transplantation: an international perspective

FULL REVIEW

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ABSTRACT

In this position article, DESCARTES (Developing Education Science and Care for Renal Transplantation in European States) board members describe the current strategies aimed at expanding living and deceased donor kidney pools. The article focuses on the recent progress in desensitization and kidney paired exchange programmes and on the expanded criteria for the use of donor kidneys and organs from donors after circulatory death. It also highlights differences in policies and practices across different regions with special regard to European Union countries. Living donor kidney paired exchange, the deceased donor Acceptable Mismatch Programme and kidneys from donors after circulatory death are probably the most promising innovations for expanding kidney transplantation in Europe over the coming decade. To maximize success, an effort is needed to standardize transplant strategies, policies and legislation across European countries.

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INTRODUCTION

Kidney transplantation (KT) avoids the debilitating effects of long-term maintenance dialysis and has been recognized as the best treatment of end-stage renal disease (ESRD). However, the shortage of organs and the barriers to access in many geographical areas have prevented growth of this therapy. In this position paper, DESCARTES (Developing Education Science and Care for Renal Transplantation in European States) board members describe current strategies for expanding living and deceased donor kidney activity. The article focuses on the recent progress in desensitization and paired kidney exchange programmes and on the use of expanded criteria donor (ECD) kidneys and of organs from donors after circulatory death. It also highlights differences in policies and practices across different regions with special reference to European Union (EU) countries.

STRATEGIES FOR EXPANDING THE LIVING DONOR POOL

Traditionally, over 50% of potential living donors otherwise suitable for donation did not proceed because immunologic screening of the recipient revealed circulating donor-specific ABO antibodies (up to 30% of donors) or human leucocyte antigen (HLA) antibodies [1]. In the new millennium, major advances have overcome these barriers.

KT from ABO-incompatible living donor

ABO-incompatible (ABOi) living donor kidney transplantation (LDKT) programmes have been successfully established in achieving patient and graft survival rates comparable to those of ABO-compatible KT [2]. In 1989, drawing on the positive experience gained in Belgium in the 1980s [3], the largest programme of ABOi-LDKT carried out so far was started in Japan with a therapeutic protocol including pretransplant splenectomy [2]. Studies in the USA published between 2004 and 2005 provided fresh impetus to ABOi-LDKT, by showing that equally satisfactory results could be obtained using the monoclonal anti-CD20 antibody, rituximab, instead of splenectomy [4]. Further studies suggested that neither splenectomy nor rituximab were absolute prerequisites [5]. Exploiting the experience gained in the USA, the Karolinska Institute in Stockholm designed a new protocol that yielded for the first time 'identical' results in terms of graft survival, graft function and complication rates of ABOi to those of ABO-compatible KT [6]. This protocol was subsequently adopted, with minor variations, in many other European centres. The main disadvantage of ABOi-LDKT is its cost, which might be considered as prohibitive in low-income countries. Nonetheless, compared with dialysis expenses, ABOi-LDKT remains cost-effective [6, 7]. The increased cost of ABOi-LDKT pertains to treatment that can be safely omitted in recipients with low anti-A/B titre (e.g. ≤1:64), such

as selective or non-selective immunoadsorption in place of standard or double filtration plasmapheresis [8]. Moreover, prolonged hospital stay is unnecessary in patients with low anti-A/B titre. Finally, many centres have abandoned the use of other expensive and virtually useless drugs, such as i.v. immunoglobulins [8, 9]. In fact, patients with low starting titre, who may receive the least costly treatments, represent more than a half of all potential candidates for ABOi-LDKT [8]. Alternatively, these patients can also be included in a paired-donor exchange programme (see below).

KT from HLA-incompatible living donor

Starting in 1998, HLA-incompatible (HLAi) LDKT programmes [i.e. renal transplantation in a recipient with a positive complement-dependent cytotoxic (CDC)- or flow cytometric-crossmatch against the donor] have been developed mostly in the USA using protocols similar to those used for ABOi-LDKT [10]. The long-term results showed that US patients who received HLAi-LDKT had a significant survival benefit compared with HLA-sensitized patients, who remained on the transplant waiting list [10]. However, compared with standard HLA-compatible LDKT, HLAi-LDKT carries an increased risk of acute antibody-mediated rejection, transplant glomerulopathy and graft failure [11, 12] jeopardizing the long-term success of transplantation. Most importantly, the risk of death is not negligible [10]. Because dialysis survival is better in Europe [13] and many European patients have access to an Acceptable Mismatch Programme (see below), European sensitized wait-listed patients may have a different risk–benefit assessment compared with the USA [14]. Unlike the strategies based on antibody removal, those based on administration of eculizumab, an anti-C5 monoclonal antibody that prevents the formation of the membrane attack complex, were shown in one series to be associated with a remarkably low risk of acute antibody-mediated rejection, although transplant glomerulopathy occurred in 25% of the patients after 2–3 years [15, 16]. In the same series of patients, eculizumab was successfully withdrawn 4 weeks after transplantation in 50% of the patients (after the administration of sixteen 300 mg vials, at a price of about 110 000 euros per patient), whereas 15% of the patients were still receiving eculizumab therapy 1 year after transplantation [15]. Therefore, the costs of protocols based on eculizumab may currently be unaffordable in most European and non-European countries. Moreover, the implementation of any HLAi-LDKT, whatever the treatment strategy used, requires costly antibody monitoring, including repeated crossmatches.

Paired kidney donation

Paired kidney donation (PKD) is when two or more living kidney donor/recipient pairs, who are not compatible with each other because the recipient has circulating HLA- and/or ABO antibodies against his/her own donor, exchange the kidneys in such a way that recipients receive compatible kidneys. PKD avoids the costs and complications of desensitization therapies for ABOi- and HLAi-LDKT.

There are several ways in which a PKD programme can be organized. The simplest one is to perform two-way paired donation between two or three incompatible pairs. To avoid the

possibility that after one donor has given a kidney to the other pair's recipient, that recipient's co-registered donor may refuse to donate in return, paired-donor transplant operations should be performed simultaneously. This type of programme (i.e. short chains and simultaneous paired donation), which was originally implemented in the Netherlands, has been shown to be successful and safe [17]. Following the Dutch experience, an equally efficient programme has been implemented in the UK [18]. Other countries such as Spain, France, Italy, Czech Republic, Austria, Belgium, Switzerland, Poland and Scandia transplant have already started a programme or are striving to implement one.

As an alternative to the Dutch model, the number of pairs may be increased by constructing a chain of organ exchanges that involves up to a dozen pairs [19]. Because it is impractical to perform all the exchanges simultaneously, they are usually accomplished in clusters over time. Here, the donor at the end of each cluster of transplantations serves as a 'bridge donor' to extend the interrupted chain of transplants at a later time [19, 20]. The most controversial issue is whether paired donors can or should be trusted to donate a kidney after their own co-registered recipients have already received a transplant [19]. In fact, 5% of paired donors eventually decline to donate. However, the possibility that after donation the co-registered recipient does not eventually receive a kidney is prevented by altruistic donation (i.e. non-directed donation to an unknown person for reasons of altruism) [19]. In fact, when altruistic donation initiates a chain of transplantations, each subsequent donor makes the donation only after the co-registered recipient has already received a transplant [19]. At the end of such chain, the last donor donates to the most suitable recipients on the waiting list or serves as a 'bridge donor' for a future transplant chain [19, 20]. This strategy is known as non-simultaneous extended altruistic donor (NEAD) chains [19]. For a potential altruistic donor, the benefit of starting such a long chain of KT may be a strong motivating factor.

It has been shown that the matching success of incompatible pairs increases with the size of the pool [20, 21]. Therefore, large national or even international registries may be needed to create efficient PKD programmes [22]. In the USA, as well as single-centre independent PKD programmes, there are also competitive non-profit registries such as National Kidney Registry or The Alliance for Paired Donation (http://www.paireddonation.org/), which run databases and allocation programmes to achieve better HLA matching while involving most available donor–recipient pairs. The Alliance for Paired Donation has already performed an international exchange with Greece, and another international alliance is currently being organized within Europe between Spain and Italy. It must be mentioned, however, that unfortunately legislation in some countries (e.g. Germany) may preclude the building of an Europe-wide registry.

There are several logistical challenges in PKD programmes. First, when different centres are involved, either the donor or his/her kidney will need to travel to the implanting centre. Procured kidneys may travel for several hours between coasts in the USA or theoretically between the US East Coast and Western Europe. Careful cooperation between centres will be required.

Acceptance of blood group-incompatible donors for patients with low-to-moderate anti-blood group antibody increases transplant rates in PKD programmes [23]. However, ABOi-LDKT programmes have been carried out in conjunction with PKD in many countries such as the USA, UK, Spain and the Netherlands. Recipients of blood type O with a donor of blood type A is the most common combination but has only a low chance of finding a match in the PKD pool compared with other blood type combinations. Thus, the ABOi-LDKT remains the most viable option for these patients [24]. Moreover, highly sensitized recipients [e.g. those with HLA panel-reactive antibody (PRA) >95%] have little chance of finding a match in PKD programmes [25]. These patients may benefit most from other strategies employed in highly sensitized patients, such as the Acceptable Mismatch Programme or desensitization strategies.

STRATEGIES FOR THE SENSITIZED PATIENT WITH NO LIVING DONOR AVAILABLE

Patients who develop antibodies against a large variety of HLA antigens (highly sensitized patients), because of pregnancy, blood transfusion and previous transplantation, have limited opportunity of having a compatible living donor or of receiving a crossmatch-negative organ from a deceased donor using standard allocation algorithms. The prevalence of highly sensitized patients and the strategies to address their situation vary greatly according to the continent and country [26].

Acceptable mismatch programme

The Eurotransplant Acceptable Mismatch Programme is an allocation system based on an innovative HLA typing and matching strategy that allows ~60% of highly sensitized patients (CDC-PRA ≥85%) to be transplanted within 2 years [27, 28]; however, the recipient should wait at least 2 years, as defined by the date of first dialysis, before inclusion in the programme. Acceptable HLA mismatches are HLA antigens that are mismatched at the broad HLA antigen level, but have compatible epitopes between donor and recipient at the structural level [29]. The compatible epitopes can be effectively identified using HLA Matchmaker [29]. The definition of acceptable HLA epitopes facilitates the identification of suitable donors, as many donor-specific HLA antibodies can eventually be recognized as being falsely donor specific.

On the basis of the experience and success of the Euro-transplant Acceptable Mismatch Programme, similar programmes have recently been implemented in France [30], Italy, Greece, Scandia transplant, Switzerland and Canada, although most of these countries are using different approaches for donor–recipient matching. It should be noted that 35% of human beings have rare HLA phenotypes and no suitable donor can be found even within the Eurotransplant Acceptable Mismatch Programme [31]. However, HLA phenotype frequencies vary amongst European populations, and rare HLA phenotypes in one population may be more frequent in other populations. Therefore, it is desirable that more countries within Europe participate in a common programme for

allocation of sensitized recipients. Indeed the EU supports research in this field: the EUROSTAM FP7 (www.eurostam.eu) was initiated in 2012 to determine the feasibility and advantage of implementing a Europe-wide acceptable mismatch programme.

'Overnight' desensitization in deceased-donation

Deceased-donor KT has been performed in a series of patients with a CDC-positive crossmatch by treating 9 L of plasma with immunoadsorption immediately before transplantation, and proceeding to transplantation if the crossmatch becomes negative after the first 6 L of treatment [32]. Immunoadsorption is then repeated several times after transplantation. In this series, Bartel *et al.* [32] showed that the CDC-crossmatch could become negative in over half of the attempts. For those patients who eventually underwent transplantation, five-year death-censored graft survival was ~75% [32]. However, 20% of the patients had immediate graft loss or primary non-function [32]. Besides being costly, this approach may be logistically challenging for many transplant centres and organ procurement organizations (OPOs) worldwide, because it requires that urgent immunoadsorption be performed overnight, and the allocation system delayed until the results of the post-treatment CDC-crossmatch become available.

Intravenous immunoglobulin/rituximab while on dialysis to increase deceased-donor transplantation rates

Desensitization with high-dose immunoglobulins and rituximab in sensitized patients while on dialysis may decrease circulating HLA antibodies for 3–12 months after treatment [33, 34]. This protocol has limited efficacy in highly sensitized KT candidates, because it does not significantly decrease the levels of the higher strength antibodies and is often accompanied by a rebound effect [34]. Nonetheless, Vo *et al.* [33, 35] showed that this strategy significantly increased the deceased-donor transplantation rates of sensitized patients, despite the fact that no priority was given to them on the waiting list. However, the increase in transplant rate was accomplished by introducing the concept of 'Acceptable Crossmatch', i.e. by raising the threshold for declaring a positive CDC- and/or flow cytometric-crossmatch (and/or, more recently, Luminex Single Antigen Beads test) [33, 36]. As a result, the incidence of acute antibody-mediated rejection was disproportionately high in patients with higher titre donor-specific antibodies compared with other lower risk patients [33]. In contrast, the small series of Marfo *et al.* [37], which included highly sensitized recipients only, and used the standard criteria for defining a positive crossmatch, treatment with high-dose immunoglobulins and rituximab did not increase deceased-donor transplant rates of treated patients. In conclusion, intravenous immunoglobulin (IVIG)/rituximab is a viable strategy, although it might be better suited for lower risk sensitized patients. Italy and France have started programmes that allow highly sensitized patients, receiving desensitization treatment while on the waiting list, to gain national (Italy) or regional (France) priority for allocation. On the basis of findings of Vo *et al.* [36], the IVIG/rituximab strategy is also cost-effective, but this finding needs

to be confirmed in prospective studies carried out in North America and in Europe.

STRATEGIES FOR EXPANDING THE DECEASED-DONOR POOL

Even for patients who are not sensitized, access to transplantation is limited by the increasing disparity between organ supply and demand. In an attempt to counter this trend and to manage the increasing proportion of older donors and donors with comorbidities, as well as the increasing number of elderly recipients, selection criteria for organ donors have been widened, leading to the use of donors that would have previously been deemed unsuitable.

Use of kidneys of suboptimal quality without compromising recipient's outcomes

Until the 1990s, organs from deceased donors over 55 years old were rarely used in transplantation. Thanks to the progressive improvement of the whole process of procurement and organ assessment, it became evident that age itself should not be a limiting parameter. However, the use of organs from elderly donors was associated with reduced graft function and reduced recipient and graft survival [38]. To minimize this impact, age matching criteria between donors and recipients have been adopted in most European countries reasoning that elderly recipients have shorter life expectancy independently of the lifetime provided by the graft [39]. Although somewhat shorter than the lifespan obtained with younger donors, recipients of kidneys from elderly donors still enjoy longer survival as compared with maintenance dialysis [37–40].

In the USA, despite implementation over 10 years ago of the ECD programme (the use of kidneys from donors older than 60 years or older than 50 years with at least two additional risk factors, offered with the potential incentive of earlier transplantation), the percentage of kidneys recovered but not transplanted remains over 40%. Major determinants of discard rates are biopsy findings on wedge biopsy (per cent glomerulosclerosis) and parameters of machine pump perfusion [40]. The United Network of Organ Sharing Kidney Transplantation Committee has recently approved a new allocation policy, which will be implemented by the end of 2014 [41]. It is based on the Kidney Donor Profile Index (KDPI), a numeric measure of donor quality. KDPI represents an improvement over the old ECD/standard criteria donor (SCD) dichotomy, by recognizing that not all ECD kidneys are alike. KDPI is a percentile rank, based on a number of donor risk indicators (KDPI = 85 means that 85% of donors are of better quality). Kidneys with KDPI > 85% are offered to a wider geographic area to promote broader sharing and to maximize utilization. Transplant programmes may choose to accept kidneys of different quality, depending on the age and the medical circumstances of each particular candidate, by establishing candidate-specific KDPI acceptability thresholds (http://optn.transplant.hrsa.gov).

It should be noted that discard rates are much lower in Europe compared with the USA [42]. In the beginning of 1999, the Eurotransplant foundation initiated a specific

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allocation scheme entitled the Eurotransplant Senior Programme (ESP) for donor kidneys older than 65 years [43]. These kidneys are primarily allocated locally to wait-listed recipients older than 65 years in order to reduce cold ischaemic time and the rate of delayed graft function with the disadvantage of imperfect HLA matching. The main goal was to derive the most benefit from these marginal organs in terms of patient survival and to reduce the waiting time in elderly wait-listed patients. Indeed, it has been shown that graft and patient survival in participants of the ESP programme is not inferior to that of elderly recipients receiving a younger graft allocated through the routine Eurotransplant Kidney Allocation System (ETKAS) algorithm [44]. In other countries, primarily Italy, the standardized assessment of a pre-transplant formalin-fixed biopsy is the key criterion by which the allocation of marginal donor organs is determined. It serves to establish which kidneys should be discarded or accepted, but also which kidneys should be allocated for dual transplantation [45]. Suitable kidneys from donors aged 65 years or above can be allocated to younger donors, within pre-defined limits of donor–recipient age difference (e.g. ±15–20 years). However, histologic scores are logistically difficult to implement in the allocation algorithm of most OPOs worldwide. Furthermore, the standardized assessment of pre-transplant formalin-fixed biopsy specimens requires a minimum of 4–5 h and may increase cold ischaemia times. Moreover, because results may show a great deal of variation between pathologists, it is advisable that OPOs have their own centralized pathological laboratory, with on-call pathologists 7 days a week.

Donation after circulatory death

Until the early 1990s, only brain-dead donors were considered suitable for transplantation. Among other regions in Europe, a group from Maastricht in the Netherlands re-introduced the concept of donation after circulatory death (DCD), which was practiced in some OPOs in the USA up to the late 1960s. After approval of DCD by the World Health Organization in 2011, DCD became more and more accepted, and allocation of DCD organs is now routine practice in 10 of the 27 European Union countries as well as North America, some countries in South America, Australia and Japan [46]. A precise pathway on organ donation including DCD was published recently [47]. Currently, there are five categories of DCD donors in the 2003 modified Maastricht classification [46]. The first two categories refer to donors who died unexpectedly, death being declared on arrival at the hospital or after unsuccessful resuscitation. These donors are predominantly used in France and Spain [46]. However, most countries use the remaining three categories of donors that refer to instances when death is anticipated, and donation occurs soon afterwards. This condition, called 'controlled' circulatory death, may take place in an intensive care unit or a special care unit [46]. In controlled donation, the techniques for organ reperfusion are easier, whereas in uncontrolled circulatory death the procedures are more demanding [48]. Various factors explain the different DCD practices across different countries. Among the most important factors are different legislations concerning consent for organ donation (presumed versus explicit consent), and different

attitudes and regulations concerning the withdrawal of futile life-sustaining treatments. Furthermore different national legislations exist concerning the length of the 'no touch' period after declaration of death and initiation of organ retrieval (e.g. 20 min in Italy versus 2–5 min in many other countries). Donation after circulatory death is prohibited in Germany. In the USA, the proportion of DCD donors is roughly 10%, but there is large international variability. In the UK, where controlled DCD donors represent 40% of the deceased donor pool, the waiting list has shown a small decline, despite a plateauing of brain-death donors and living donors and a constant rate of newly wait-listed patients [49].

CONCLUSIONS

KT is the best renal replacement therapy modality for most patients, but organ shortage and blood group or HLA incompatibility still limits access to this treatment. Some classical barriers to KT, such as those due to blood type incompatibility, have largely been overcome. However, despite the cost-effectiveness of these techniques compared with dialysis, their availability varies across different countries. Highly sensitized patients for whom immunologically suitable donors may be difficult to find might be best considered in allocation schemes such as the Acceptable Mismatch Programme. Among the initiatives to increase KT, living donor paired exchange and kidneys from donors after circulatory death are probably the most promising sources of organs and ways to expand KT in Europe over the coming decade. To ensure success, an effort is required to standardize transplant strategies, policies and legislation across European countries.

CONFLICT OF INTEREST STATEMENT

None declared.

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