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Hypersensitized candidates to kidney transplantation in Portugal

Candidatos hipersensibilizados a transplantação renal em Portugal

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ABSTRACT

The presence of donor specific anti-HLA antibodies is generally a contraindication for transplantation and nowadays the identification of these antibodies are part of most pre-transplantation evaluations. In Portugal, the implemented protocol for registration and maintenance of the active list for kidney transplant includes a complement-dependent cytotoxity (CDC) panel-reactive antibody (PRA) screening method, and Luminex technology for detecting and characterizing HLA alloantibodies. Under the current Portuguese kidney allocation system from deceased donors, implemented in August 2007, deceased donor kidneys are primarily allocated via ABO identical and time on dialysis with extra points to hyperimmunized patients, namely PRA CDC › 50%. Additional risk for the candidate or transplant organ can be represented by a proposed calculated PRA (cPRA) based upon unacceptable HLA antigens detected by Luminex to which the patient has been sensitized. These unacceptable HLA antigens used to generate cPRA represents a 'virtual' crossmatch (XM). Sensitized patients are less likely to be matched with a suitable donor organ. Even after clearing the hurdle of procuring a living donor, it is still possible that this is not sufficient due to the likelihood of having an XM-positive. In such cases, and in the presence of incompatible blood type between recipients and their intended living donors, kidney paired donation (KPD) can provide an answer to this catch by facilitating exchanges between willing donors' kidneys. A national Portuguese KPD programme, when realized, may prevent the current loss of a significant number of suitable living donors and reduce waiting list time for a deceased donor. An upgrade of a suggested point system in a Portuguese KPD programme will be the use of cPRA instead of the values of PRA CDC. In Portugal, the virtual XM approach just represents the optimization of an existent technique.

RESUMO

A presença de anticorpos anti-HLA específicos do dador é geralmente uma contraindicação para transplante e, hoje em dia, a identificação destes anticorpos é parte de muitos protocolos de avaliação pré-transplante. Em Portugal, o protocolo implementado para o registo e manutenção em lista activa para

transplante de rim, inclui um método de pesquisa em painel reactivo de anticorpos (PRA) por citotoxicidade dependente do complemento (CDC) e a tecnologia Luminex para detectar e caracterizar aloanticorpos HLA. Segundo as actuais normas para a selecção do par dador-receptor em homotransplantação com rim de cadáver, implementadas em Agosto de 2007, a distribuição destes órgãos é prioritariamente isogrupal, contabilizando o tempo em diálise com pontos extra paras doentes imunizados, nomeadamente PRA CDC› 50%. Um risco adicional para os candidatos a transplante de órgãos pode ser representado pelo proposto PRA calculado (cPRA), que tem por base antigénios HLA não aceitáveis, detectados por Luminex e para os quais os doentes estão sensibilizados. Estes antigénios HLA não aceitáveis usados para gerar o cPRA representam um crossmatch (XM) virtual. Os doentes sensibilizados têm uma menor probabilidade de encontrar um dador de órgãos admissível e mesmo depois de ultrapassada a barreira de encontrar um dador vivo disponível, é possível que isto não seja suficiente devido ao risco elevado de ter um XM positivo. Nestes casos e quando há incompatibilidade ABO entre um receptor e o seu potencial dador vivo, a troca de dadores vivos de rim (TDR) pode ser a resposta a este problema facilitando a consumação de transplantes compatíveis. Um programa nacional de TDR, quando implementado, pode evitar o actual desperdício de possíveis dadores vivos de rim e potencialmente reduzir o tempo de espera em lista para transplante com dador cadáver. Uma melhoria a um sugerido sistema de pontuação num programa Português de TDR será a utilização do cPRA em substituição dos valores de PRA CDC. Em Portugal, a abordagem de XM-virtual apenas representa a optimização de técnicas já existentes.

INTRODUCTION

The demand for kidneys for transplantation grows daily due to the successful treatment of many patients with end stage renal disease. The limited number of organs available for transplantation requires that their distribution be made as equitable as possible in order to optimize the use of this scarce resource. A fair and appropriate distribution of available organs for transplantation continues to be a relevant issue and an important topic of debate. If the utilitarian argument for the distribution of organs argues that they should be transplanted in candidates predicted to live longer, then the argument of justice or fairness requires that all transplant candidates have equal opportunity of transplantation.

The success of kidney transplants depends largely on genetic and immunological compatibility between the organ and its recipient. An important barrier to kidney transplantation is the sensitization of transplant candidates to human leukocyte antigen (HLA). Anti-HLA antibodies develop after exposure to HLA antigens, typically following a blood transfusion, pregnancy, or a previous transplant. And, many hypersensitized patients do not find an acceptable donor for transplantation, remaining on dialysis indefinitely.

DONOR SPECIFIC ANTIBODIES

Pre-existing HLA donor specific antibodies (DSA) are known to be significant determinants of kidney transplant outcome[1].

The presence of DSA anti-HLA is generally a contraindication for transplantation and, nowadays, the identification of these antibodies is part of most pre-transplantation evaluations[2]. The presence of preformed HLA DSA has been associated with higher risk for hyperacute rejection, accelerated acute rejection, antibody-mediated rejection, delayed graft function[3] and lower allograft survival[4]. These findings have lead clinicians to periodic DSA screening of all transplant recipients in order to discover those presenting these antibodies[5].

Several techniques are available to detect these DSA. Luminex (Luminex, Austin, Texas, USA) is a solid-phase assay using micro-spheres and is more sensitive to detect HLA antibodies than conventional tests. Luminex mean fluorescence intensity (MFI) as a measurement of DSA strength can predict positive crossmatch results[6]. Eventually, results using this method could aid in the stratification of immunological risks lending added qualification during the clinical decision-making process[7].

In Portugal, the regulatory circular 01/DQS, of the 7th January 2009, issued by the Directorate General of Health, defines the protocol for the registration and maintenance of active list candidates for kidney transplantation in both the initial evaluation of patients (ABO blood group and HLA typing) and in its quarterly review. This protocol includes a complement-dependent cytotoxicity (CDC) panel--reactive antibody (PRA) screening method, and Luminex technology for detecting and characterizing HLA alloantibodies.

Hyper-sensitized patients have lower chances of transplantation once they are more likely to have a positive crossmatch (XM) with an available donor for kidney transplantation. The undesirable effects of broad allosensitization can be minimized by many complementary approaches, such as: kidney paired donation (KPD), priority allocation on the deceased donor waitlist, and/or desensitization or XM conversion[7].

The current Portuguese kidney allocation system from deceased donors was implemented in August 2007 (Ordinance no. 6537/2007 of 3rd April). Under this allocation system, deceased donor kidneys are primarily allocated via ABO identical and a scoring criteria as following: hyper-immunized patients, namely PRA CDC › 50% as 4 and › 80% as 8 points; time on the waiting list as 0.1 points/month; and for HLA mismatches from 12 (without mismatches) to 1 point (more than two mismatches).

Additional risk for the candidate or transplant organ can be represented by a proposed calculated PRA (cPRA) based upon unacceptable HLA antigens to which the patient has been sensitized [3]. It would be a more accurate measure for the definition of hyper-immunized patients, according to the protocol implemented for Portuguese kidney transplant candidates. This proposed cPRA is calculated with HLA antigen frequencies of kidney donors and represents the percentage of donors that express one or more of the antigens unacceptable for a given transplant candidate[3]. In Portugal, a cPRA can be calculated with HLA antigen frequencies of voluntary bone marrow donors[8], because most (if not all) donors are in fact potential deceased organ donors and because their HLA frequencies are already available[9].

The cPRA gives us the probability of each transplant candidate to have an XM-positive with the next available deceased donor for kidney transplantation. Thereby, those patients with higher probabilities should receive extra points in the Portuguese allocation system for kidney transplantation with deceased donors. Even better than determining a probability of an XM-positive, is knowing whether or not a candidate will have a definite XM-positive with the available donor in real-time. The unacceptable HLA antigen, against which the recipient has antibodies, used to generate cPRA represents a 'virtual' crossmatch (XM)[10]. With the implementation of these measures, money and time will be saved by not performing some real XMs at allocation of the deceased donors.

VIRTUAL CROSSMATCH

The virtual XM is based on the characterization of acceptable HLA mismatches in pre-sensitized recipients and reflects an attempt to increase the donor pools and eliminate the need for a conventional XM[6].

In order to calculate the likelihood of a suitable XM-negative transplant, it is paramount to obtain a detailed characterization of individual HLA antibody profiles[7].

In Eurotransplant kidney allocation system (ETKAS) a special program was established in order to manage highly immunized patients (PRA CDC › 85%), the Acceptable Mismatch (AM) programme. This programme identifies HLA antigens against which the patient waiting for a transplant has not yet developed allo-antibodies and, therefore, is less likely to have a positive XM. Luminex based antibodies specificities are excluded from the AM programme because it would result in a huge increase in the number of highly sensitized patients, affecting the exceptionality of the programme[11].

For the implementation of the cPRA, an MFI threshold for defining unacceptable antigens should be set. Although definition of a cutoff for evaluation of the strength of anti-HLA antibodies through Luminex MFI can be controversial, it is an essential tool in virtual XM.

Pre-transplant DSA HLA antibodies with MFI values above 1000[12] had been proposed as high risk for

transplantation and an MFI value higher than 1500 for DSA has been shown to have a statistical impact in graft survival[4].

Even though the use of cPRA and virtual XM raises undeniable issues, it is also the benchmark of instrumental advancement in organ allocation algorithms, including the definition of appropriate threshold values for antibody assignment and recognition of relevant antibodies also to HLA-Cw*, HLA-DQ*, and HLA-DP*.

However, the utility of virtual XM does not replace the requirement for actual XM testing before transplantation, to attest the inexistence of immunologic incompatibility.

LIVING DONOR TRANSPLANT

Living donor transplants have been documented as a better solution for end stage renal disease (ESRD) patients when compared with deceased donor transplants[13]. Also, for living donors, risks are minimal due to technical improvements.

Despite improved graft function and longevity, live donor kidney transplants (LDKT) are only a moderate portion of kidney transplants performed in Portugal[14].

Knowledge of how to ask someone to donate was one of the barriers identified by transplant candidates[15] to LDKT. The unwillingness of the candidates to seek potential donors or their inability to motivate these donors[16] is other identified barrier. Concerns surrounding donor morbidity have also been noted in patients with ESRD[15]. It has been indicated that having former donors speaking to potential donors could assuage these concerns, thereby improving LDKT numbers[17].

Older ESRD patients and those with low-income have been indicated as being less likely to have a potential living donor. On the other hand, greater self-efficacy (defined as a person's belief in their capabilities to attract a donor) was a strong predictor for having a potential living donor[16].

To further boost living kidney donation, measures have been proposed to tackle the aforementioned issues affecting recipients and donors pre- and post-transplant fears and for alleviating patients guilt. Educational programmes have been implemented to raise awareness about living kidney donation and its benefits while at the same time coaching patients through asking for a donation[15].

Sensitized patients are less likely to be matched with a suitable donor organ just via the Portuguese allocation system for deceased donors. After clearing the hurdle of procuring a living donor, it is still possible that this is not sufficient due to the likelihood of having an XM-positive. In these cases and in the presence of incompatible blood type between recipients and their intended living donors, kidney paired donation (KPD) can provide an answer to this catch by facilitating exchanges between willing donors' kidneys[18].

A large pool of incompatible donor-recipient pairs promotes better matching outcomes while maximizing pool size for the establishment of national KPD programmes. Also, a central coordination and a central laboratory responsible for immunological study of donors and recipients are guarantees of success for such kinds of programmes[19].

A national Portuguese programme, when realized, may prevent the current loss of a significant number of suitable living donors and, thereby, have a significant impact in reducing waiting list time for a deceased donor[18]. An upgrade of a suggested point system in a Portuguese living donor exchange programme[19] will be the use of cPRA instead of the values of PRA CDC.

Applying virtual XM rules in KPD has been suggested[20]. The HLA antibody at a strength of › 2000MFI and listing in the pool donor HLA antigens and recipients HLA antibodies at high-resolution level are recommended when using virtual XM in KPD[20]. Virtual XM in KPD will reduce the number of matched pairs having a positive crossmatch (using both CDC or flow cytometry techniques) and, therefore, reduce the number of breakdown chains.

CONCLUSIONS

The Virtual XM approach in combination with cPRA represents progress when dealing with hypersensitized

patients waiting for a kidney transplant, particularly in kidney transplantation with living donors, where donors and patients can be HLA genotyped at high--resolution level. Also, with the implementation of a KPD programme in Portugal, virtual XM will be vital to assure its success. In Portugal, the virtual XM approach only represents the optimization of an existent technique.

Conflict of interest statement. None declared.

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