Red cell and human leukocyte antigen alloimmunization in candidates for renal transplantation: a reality

Mariza Aparecida Mota

[1]Instituto Israelita de Ensino e Pesquisa, Hospital Albert Einstein – IIEPAE, São Paulo, SP, Brazil

Alloimmunization is defined as an immune response to foreign antigens after exposure to genetically different cells or tissues. Although alloimmunization is a natural event during pregnancy, frequently it is the undesirable outcome of a blood transfusion and/or transplant. The reaction of the recipient's immune system will depend on genetic and acquired factors related to the recipient and to antigen immunogenicity. The incidence of human leukocyte antigen (HLA) and/or red cell alloimmunization is high in chronically transfused patients, such as those with hemoglobinopathies, myelodysplastic syndromes, chronic renal disease and others[1].

Around 100,000 patients are on waiting lists for renal transplantation in the USA, 30% of whom are already sensitized to allogeneic HLA antigens. In the UK, 23% of the patients listed for a first transplant and 52% waiting for a re-transplant have anti-HLA antibodies[2].

In 2005, non-sensitized patients in the USA whose panel reactive antibody (PRA) was 0% at the moment that they were included on the list had a waiting interval of around 2.5 years, while those with PRAs ranging from 1-19% and 20-79% had to wait for an average of 2.9 and 4.4 years, respectively in order to get a suitable organ. Highly sensitized patients whose PRA was over 80%, have to wait a long time to get a compatible graft; the number of patients in this condition has virtually doubled in the last five years, from 7.5% to 13.3%. When sensitized patients undergo transplantation, the presence of preformed HLA antibodies is associated with a greater risk of an early or late graft loss. It is harder to find a compatible organ for these patients, who are kept on a chronic dialysis program and present with high mortality rates, with consequently elevated costs to the health system. Therefore, sensitization is a matter of public health[3].

There is a direct correlation between a positive crossmatch and short graft survival. Therefore, it is mandatory to have a negative crossmatch before a renal transplant[3]. Over the years, the methods used to detect HLA antibodies have improved in respect to sensitivity and specificity. Crossmatching using complement-dependent cytotoxicity (CDC) aims at identifying clinically significant HLA antibodies responsible for antibody-mediated immune responses in the recipient. The solid phase methodology using fluorescent microbeads (Luminex platform) has been increasingly used to detect HLA antibodies. It allows the detection of different antibodies simultaneously and compares them with the recipient's HLA antigens. One advantage of this method is the absence of false positive results and the ability to accurately determine the antibody specificity[4-9] .

Lefaucheur et al. suggest that the presence of donor-specific HLA antibodies correlates with a high incidence of antibody-mediated graft rejection and a shorter graft survival. Moreover, another factor that contributes to a short graft survival in renal transplants is the development of new HLA antibodies[5].

Thiyagarajan et al. analyzed the clinical significance of the presence of HLA antibodies and donor-specific antibodies before transplant and their impact on graft function, rejection episodes and graft survival. Using the solid phase technology with microbeads with 141 patients, he found class I HLA antibodies in 35 patients (24.8%), class II HLA antibodies in 23 patients (16.3%) and donor-specific antibodies in 33 patients (23.4%). The glomerular filtration rate was similar in the three groups independent of the presence of antibodies. However, there was a high rate of acute rejection confirmed by biopsy after one year in the group with class I HLA antibodies and in patients with donor-specific antibodies[3].

Data published in the last meeting of the National Kidney Foundation in May 2012 suggest that the risk of alloimmunization by blood transfusion is substantial. In this report, risk factors to develop a PRA > 80% were assessed. As compared to patients who had never been transfused, the odds ratio for patient sensitization after blood transfusion in any disease stage with a PRA > 80% was 2.38. In this analysis, the risk to become highly sensitized at the moment of transplant was higher in men compared to women. Several studies have shown that leukoreduced blood does not prevent alloimmunization in patients who undergo transplants, as well as in candidates for renal transplant[6].

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Corresponding author:
Mariza Aparecida Mota
Instituto de Ensino e Pesquisa Albert Einstein
Av Albert Einstein 627 sala 487 Morumbi
05651-901 – São Paulo, SP, Brazil
Phone 55 11 3747-0444
mariza.mota@einstein.br

www.rbhh.org or www.scielo.br/rbhh

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In this issue of the Revista Brasileira de Hematologia e Hemoterapia, da Silva et al. have published an interesting study about HLA and red cell alloimmunization in patients awaiting renal transplants in the northeast of Brazil[7]. Of the 393 patients with chronic renal disease included in the study, 132 (33.6%) were alloimmunized, 78% of whom had anti-HLA antibodies, 9.1% red cell antibodies and 12.9% antibodies against both HLA and red cell antigens. Buetens et al. studied 53 male patients with red cell antibodies, 22.6% of whom also had HLA antibodies. In contrast, only 10.1% of the 69 patients in a control group had HLA alloimmunization[8].

Zalpuri et al. reported an alloimmunization rate of 1-6% after a single transfusion episode in the general population, while in multitransfused patients, this figure rises to > 30%[9]. This can lead to clinical complications, such as delayed hemolytic transfusion reactions and difficulty to obtain compatible blood units in due time.

Cruz et al. studied 3044 multitransfused patients and found irregular antibodies in 227 (7.5%) with antibodies against the Rh system (anti-E, -D, -C) and Kell (anti-K) or a combination of these being the most common.[10] da Silva found concordant results, with a higher incidence of antibodies against the Rh system[7].

It is worth mentioning that most of the antibodies described are clinically significant and may cause acute or delayed transfusion reactions. One complicating factor is that around 50% of the red cell antibodies may become undetectable over the years and are thus capable of causing hemolysis even with negative panel results.

One of the current strategies to prevent red cell alloimmunization in patients on chronic blood transfusion regimes is complete erythrocyte compatibility. This can be achieved by genotyping patients and blood donors on a large scale, so as to provide phenotype-compatible units with respect to blood groups with clinical importance.

Alloimmunization against red cell and HLA antigens in candidates for renal transplants is a reality[11]. New strategies to investigate and manage alloimmunized patients are needed to allow for advances in renal transplantation and minimize the waiting time for candidates. Knowledge on the reality of sensitization against red cell and HLA antigens in our population constitutes a first step in this direction.

References

1. Zimring JC, Welniak L, Semple JW, Ness PM, Slichter SJ, Spitalnik SL; NHLBI Alloimmunization Working Group. Current problems and future directions of transfusion-induced alloimmunization: summary of an NHLBI working group. Transfusion. 2011;51(2):435-41.
2. Montgomery RA, Zachary AA. Transplantation: All for one and one for all – alloimmunization and polyreactivity. Nature.2012;8(8):442-3.
3. Thiyagarajan UM, Bagul A, Frost J, Horsburg T, Nicholson ML. Role of human leukocyte antigen , donor-specific antibodies, and their impact in renal transplantation. Transplant Proc. 2012;44(5):1231-5.
4. Tait BD, Susal C, Gebel HM, Nickerson PW, Zachary AA, Claas FH, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non HLA antibodies in transplantation. Transplantation. 2013:95(1):19-47.
5. Lefaucheur C, Loupy A, Hill GS, Andrade J, Nochy D, Antoine C, et al. Preexisting donor specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol. 2010;21(8):1398-406.
6. Macdougall IC, Obrador GT, El Nahas M. How important is transfusion avoidance in 2013? Nephrol Dial Transplant. 2013:28(5):1092-9.
7. Silva SF, Ferreira GM, Silva SL, Alves TM, Ribeiro IF, Ribeiro TR, et al. Red blood cell and leukocyte alloimmunization in patients awaiting kidney transplantation. Rev Bras Hematol Hemoter. 2013;35(3)185:8.
8. Buetens O, Shirey RS, Goble-Lee M, Houp J, Zachary A, King KE, et al. Prevalence of HLA antibodies in transfused patients with and without red cell antibodies. Transfusion. 2006;46(5):754-6.
9. Zalpuri S, Zwaginga JJ, van der Bom JG. Risk factors for alloimmunization after red blood cell transfusions (R-FACT): a case cohort study. BMJ Open. 2012;2(3):1-7.
10. Cruz RO, Mota M, Conti FM, Pereira RA, Kutner JM, Aravechia MG, et al. Prevalence of erythrocyte alloimmunization in polytransfused patients. einstein (São Paulo). 2011;9:173-8.
11. Higgins R, Krishnan NS, Zehnder D. Briggs D. Human leukocyte antigen antibody incompatible renal transplantation. Indian J Nephrol. 2012;22(6);409-14.

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