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ABO-Incompatible Kidney Transplantation: Past, Present and Future

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Introduction

Kidney transplantation (KTx) is the treatment of choice for end-stage renal disease [1]. Compared with dialysis it confers a survival advantage, enhances quality of life and is more cost-effective. There are two types of potential donors in renal transplants: deceased and living donors. Transplantation from living donors provides better survival rates in comparison to those from deceased ones [2]. Furthermore, transplantation from living donors could be the solution for the shortage of cadaveric donated organs. Unfortunately, for many years a significant number of potential living donors were rejected due to blood group incompatibility with the recipient. ABO-incompatibility was considered to be an absolute contraindication to transplantation. However, during the last 15years the implementation of new transplant protocols has significantly diminished this barrier and has lead the way for the induction of ABO-incompatible (ABOi) transplantation worldwide.

History of ABO-incompatible kidney transplantation

The first successful ABOi transplantations were reported by Alexandre, *et al*. in 1987 [3]. These transplantations were performed using living donors, splenectomy, plasmapheresis and an immunosuppressive regimen with cyclosporine, steroids, azathioprine and antilymphocyte globulin. Further development in the field of ABOi KTx came from centers in Japan. With the use of plasmapheresis or double filtration plasmapheresis for removing anti-ABO antibodies, splenectomy for physically removing the source of the antibody-producing cells and new pharmacological immunosuppressants, the Japanese group presented significantly improved graft survival [4]. Based on these promising results, in the first decade of this millennium ABOi KTx began to expand slowly and in other centers of USA and Europe. However, many institutions approached the need for splenectomy with a degree of skepticism, considering the related long-term infections and the increased surgical risk. The concept of a "medical splenectomy" with the introduction in clinical practice of Rituximab-a monoclonal antibody against CD-20 on B cells- made ABOi KTx more feasible [5]. Also, the introduction of new immunoadsorption techniques with the use of specific anti-A or anti-B immunoadsorption columns (Glycosorb®), which effectively and specifically depletes anti-A or anti-B antibodies without any apparent side effect, made transplantation preconditioning easier. Nowadays, ABOi KTxs are worldwide performed with remarkable outcomes.

Current desensitization protocols and long - term outcomes

Although there are some differences in the desensitization protocols among different transplant centers, most include a combination of plasmapheresis or immunoadsorption, intravenous immunoglobulin and a triple-drug immunosupression consisting of tacrolimus, mycophenolate and prednisolone. In addition, monoclonal or polyclonal antibody agents are used during the induction period. Splenectomy is still in use selectively, while rituximab administration is in use. After transplantation, close monitorring of the ABO antibody titer is necessary and usually some more plasmapheresis sessions are needed to eliminate the antibodies rebound. The major determinant of successful graft outcome is the prevention of hyperacute rejection and the establishment of accommodation as early as possible. Accommodation is defined as the absence of antigen-antibody reaction, despite the presence of "foreign" antigen on the vascular endothelial cells of the graft and the presence of antibody in recipient's blood [6]. Independently of the different protocols that are used in various centers, the short-and long-term outcomes of ABOi transplantations are now comparable with those of ABO-compatible KTxs. In Japan during the past two decades, about 2000 ABOi KTxs were performed. The patient and graft survival rates for the 1427 procedures performed after 2001 were 98% and 96% for the first year and 91% and 83% for 9 years respectively [7]. In the USA, the outcomes were also excellent with patient and graft survival of 89,4% and 89%, respectively reported by the Johns Hopkins University after 5 years follow-up. [8]. From Europe, the results of a Swedish Group for 3 years follow-up were 100% for patient survival and 86,7% for graft survival [9]. Also, the Melbourne Group reported 100% patient and graft survival after 2,2 years of follow-up [10].

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At our center, we have performed 30 ABOi kidney transplantations since 2005. Pre-transplant desensitization was made according to an amendment of the Swedish protocol. More specifically we have used repeated immunoadsorptions mostly with the Glycosorb ABO-collumns or in combination with the Immusorba-collumns to achieve an isoagglutinin titer of $\leq$ 1:16 at the day of transplantation, intravenous immunoglobulin 0.5g/kg of body weight at the end of immunoadsorptions course, rituximab 375mg/m^2 body surface area on day 20 pre-transplantation, and oral immunosupression instituted a week prior to KTx. As induction therapy monoclonal antibodies against interleukin-2 were used, while at least three immunoadsorption sessions were performed postoperatively depending on anti-A/B titers thereafter. The main difference from the Swedish protocol was the use of everolimus or mycophenolate acid in the triple-drug combination with tacrolimus and corticosteroids. One-year patient and graft survival rates were 100%, while the 5-year patient and graft survival rates were 91,7%. In comparison with the ABO-compatible KTxs we did not observe differences in the incidence of viral or bacterial infections.

Futures expectations

Since many centers report results comparable with conventional ABO-compatible transplants, it is obvious that ABOi transplantation is an acceptable alternative. It is an option that patients must have as it decreases the waitlist and the associated morbidity and mortality.

New techniques for antibody removal in combination with novel pharmacological agents for B-cell depletion could facilitate the preconditioning for ABOi transplantation in the future. The better understanding of incompatible kidney transplant histology and graft accommodation could also improve graft survival results and reduce the risk for rejection.

One of the remaining obstacles for ABOi KTx is the cost. The need for preconditioning prior to transplantation, post-transplant immunoadsorptions and monitoring significantly increase the cost related to ABOi KTx. However, in terms of cost-effectiveness, studies from the USA and Europe showed that, despite the increased initial mean cost of ABOi transplantation, on a long-term financial plan this turned out to be a cost saving therapy, considering the expenses associated with maintenance dialysis [11].

On the other hand paired exchange kidney donation (PKD) could be an option for some patients, especially in low-income countries. PKD allows an exchange of kidneys between two or more donor/recipient pairs that are ABOi or HLA incompatible, with the aim of achieving compatible pairs. The main problem of PKD programs is the size of donors' pool. With the creation of international networks of PKD programs, this goal could be attained. Furthermore, with the current established PKD programs in Europe, such as in the Netherlands [12] and United Kingdom [13], the implementation of this strategy seems to be more feasible.

Conclusions

Over the last two decades advances in technology and pharmacotherapy made ABOi transplantations to be a reality. ABOi KTx can now be part of daily practice in most of the transplants centers with the support of an appropriate organized laboratory, clinical and renal pathology teams. This offers a new option for end-stage renal disease patients to improve the length and quality of their life.

Conflict of interest statement. None declared.

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