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BRIEF REPORT

Optimizing HLA matching in a highly sensitized pediatric patient using ABO-incompatible and paired exchange kidney transplantation

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Abstract
Background Kidney transplantation is the treatment of choice for end-stage renal disease. However, since pediatric patients have long projected life-years, it is also optimal for them to get well-matched transplants to minimize long-term sensitization. In North America, pediatric kidney transplantation is largely dependent upon the use of deceased donor organs, making it challenging to identify timely, well-matched transplants. Pediatric recipients may have willing living donors who are either HLA- or ABO-incompatible (ABOi); therefore, one solution is to utilize ABOi transplants and paired exchange programs to enhance HLA matching and living donation.

Case-diagnosis/treatment We adopted this approach for a highly sensitized patient with cPRA 90 %, who received a successful ABOi paired exchange transplant. The recipient received pre-transplant immunomodulation until an acceptable isohemagglutinin titer <1:8 was reached before transplantation. The patient was induced with anti-thymocyte globulin and maintained on steroid-based triple immunosuppression. Eighteen-month allograft function is excellent with an estimated glomerular filtration rate (eGFR) of 83.53 ml/min/1.73 m^2. The patient did not develop de novo donor-specific HLA antibodies or have any episodes of acute rejection

Conclusions This case highlights the safety and efficacy of using paired exchange in combination with ABOi transplants in pediatric kidney transplantation to optimize HLA matching, minimize wait times, and enhance allograft survival.

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Introduction

While expedited kidney transplantation is the treatment of choice for pediatric end-stage renal disease (ESRD), it has become increasingly evident that most pediatric renal transplant recipients need more than one kidney in their lifetime. Thus, it is also optimal for them to received well HLA-matched transplants to minimize long-term sensitization. Such sensitization has been reported to make second transplants difficult in these patients [1].

In the USA, children and adolescents with ESRD have become increasingly dependent upon the use of deceased donor organs [2]. There are more than 900 children between the ages of 0 and 18 waiting for a renal transplant and the median wait time is approximately 500 days [3]. This makes it challenging to identify timely yet well-matched transplants.

One potential solution that has not been widely discussed in pediatrics is to utilize ABO-incompatible (ABOi) living-donor transplants, which has been used actively for almost 2 decades in Japan [4]. However, it has not gained comparable popularity in most other parts of the world, including the USA [5]. Additionally, the combined approach of ABOi transplantation and paired donation has not been described in pediatric transplantation. The UCLA Kidney Transplant Program adopted a protocol for ABOi kidney transplantation in adults in 2010 [6] and in children in 2011 to complement its existing paired exchange program, which was established in 2007. This report describes the first pediatric experience using ABOi renal transplantation in combination with the paired exchange program to enhance HLA matching and decrease transplant wait times.

Case report

The patient was an African–American boy who had been a candidate for a re-transplant at age 12, as his first allograft had been lost because of chronic rejection at 8 years post-transplantation. His calculated panel reactive antibody (cPRA) was>90 %. The patient's serum contained high titers of donor-specific HLA antibodies to many deceased donors. He had multiple willing potential living donors, but his sera similarly contained strong donor-specific antibody (DSA) against all that were tested. The patient had been active on the deceased donor list and receiving dialysis for 24 months when it was elected to search the US-wide National Kidney Registry (NKR) database for a HLA-compatible allograft against which the patient did not have anti-HLA class I or II DSAs. The patient's blood type was O and a blood type A donor was identified with a 7/8 HLA match. The recipients HLA typing was A2, 3; B13, 35; DR7, 13; DQ 2, 6. The donor's HLA typing was A2, 3; B13, 65; DR7, 13; DQ 2, 6. It was arranged for the patient's father to be a donor to the identified exchange recipient.

After providing informed consent, the patient was treated with a standardized protocol. Extensive pre-transplantation laboratory work was carried out. A combination of rituximab 375 mg/m^2 (Genentech Pharmaceuticals) and 2 g of IVIG (Privigen−10 % liquid IVIg; CSL Behring) was administered once 1 month before transplantation. As shown in Fig. 1, the patient's pre-transplant anti-A isohemagglutinin titer was 1:128 for immunoglobulin M (IgM), and 1:16 for immunoglobulin G (IgG). Plasmapheresis was performed, beginning 1 week before transplantation. Pre-transplantation isohemagglutinin titers were assessed during therapy, and adjustments in the plasmapheresis schedule and number of treatments was made to obtain an isohemagglutinin IgG titer of≤ 1:8 on the day of transplantation. The patient received one plasma volume exchange with 50 %/50 % saline/5 % albumin. The patient received six sessions of pre-transplant plasmapheresis to bring his titer up to 1:8 on the day of transplant. He underwent successful transplantation.

Combination treatment with tacrolimus and mycophenolate mofetil was started 1 week before transplantation. While on dialysis, the patient was given standard vaccines including protection against the encapsulated organisms (*Neisseria*, *Streptococcus*, and Hib) in the event that post-transplantation splenectomy and/or anti-C5 monoclonal antibody (eculizumab, Alexion Pharmaceuticals) were deemed necessary to salvage potentially worsening renal function and refractory antibody-mediated rejection (AMR).

Immediately before transplantation and after his final pre-transplant plasmapheresis, the patient received a combination of methylprednisolone (10 mg/kg) and anti-thymocyte globulin (1.5 mg/kg) induction. Methylprednisolone (0.5 mg/kg) was administered on postoperative day (POD) 1 and continued for at least a week before further weaning. Prednisolone was tapered to a dose of 0.1 mg/kg/day during the first 8 to

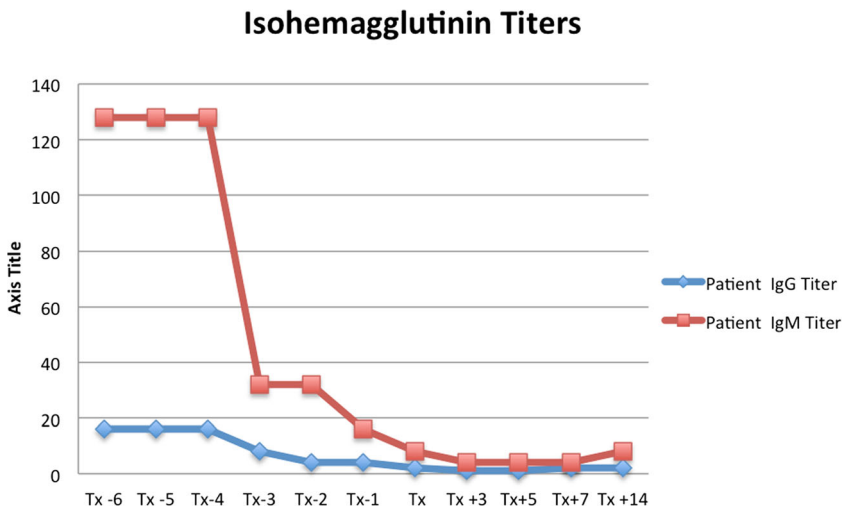

Fig. 1 **a**, **b** Immunoglobulin G (*IgG*) and immunoglobulin M (*IgM*) isoagglutinin titers pre- and post-transplantation respectively. *Tx* day of renal transplant. Plasmapheresis carried out on pre-transplantation day 4, day 3, and day 2

12 weeks. Treatment with tacrolimus/mycophenolate was restarted on POD 2. A tacrolimus level of 10 ng/ml was targeted for the first 3 months, with levels of 6–8 ng/ml subsequently. Mycophenolate mofetil dosing was 600 mg/m^2 / dose given twice daily and weaned to 450 mg/m^2/dose twice daily once therapeutic tacrolimus levels were achieved.

The graft functioned immediately without any immediate episodes of antibody-mediated rejection (AMR). Isohemagglutinin titers were determined by using the standard tube method [7]. Post-transplant plasmapheresis was performed to keep the titer at 1:8 or less in the first post-transplant week and at 1:16 or less in the second week and beyond. Measurement of titers was performed each morning, daily during the post-transplantation period while hospitalized, and at each outpatient visit during the first month post-transplantation, and monthly thereafter. As the patient's titers never increased above 1:8, he did not require post-transplantation plasmapheresis, splenectomy, or eculizumab. The patient was monitored for infection with monthly cytomegalovirus (CMV), Epstein–Barr virus (EBV) and BK viral polymerase chain reactions, and there was no increase in the incidence of infections or viremia.

The patient was seen twice weekly for the first 4 weeks, once weekly for the next 8 weeks, and every 2 weeks thereafter up to 6 months. Anti-HLA class I and II DSAs were monitored weekly for the 1st month and every month thereafter for the 1st year using the Luminex assay. Protocol biopsies were performed at 6 months and 1 year. There were no episodes of biopsy-proven AMR or acute cellular rejection (ACR) defined by the Banff criteria. Additionally, there was no development of HLA DSAs and no elevation in isohemagglutinin titers. The estimated glomerular filtration rate (eGFR) as calculated using the Schwartz equation at 1 year post-transplantation was 83.53 ml/min/1.73 m^2.

Discussion

Our patient with>90 % cPRA is particularly instructive. The patient waited in the NKR for 10 months before receiving his 5/6 HLA-compatible cross-match-negative kidney, which was blood type A, through the paired exchange program, whereas he had been waiting on the deceased donor list for 2 years. The resulting transplant course was very stable. The NKR has facilitated over 1,000 exchanges so far [8]. The use of ABOi transplantation to obviate the effect of HLA antibodies was suggested by Montgomery et al., who utilized HLA-identical ABOi sibling donors for ultra-highly sensitized recipients [9]. In addition, it has been shown recently that the use of ABOi-matching significantly enhances the transplant rates in paired kidney donation and the use of a non-related ABOi donor identified through a paired donation algorithm to achieve HLA compatibility has recently been reported in a highly sensitized adult [10, 11]. To the best of our knowledge, our case is the first case of ABOi and paired exchange being used to overcome HLA incompatibility in pediatrics. It should be noted that the patient was particularly well matched, especially for class II antigens (HLA DR and DQ). Multiple studies have shown that class II DSAs, specifically against HLA-DQ specificities, occur more commonly than HLA-DR antibodies and are highly associated with AMR and allograft failure [1, 12, 13]. By contrast, late AMR from anti-A or -B isohemagglutinin is unusual after post-transplant weeks 2–3. Thus, ABOi, in addition to paired exchange, can minimize the development of DSA and AMR.

Another interesting phenomenon is illustrated by the finding of C4d positivity on the 6-month protocol biopsy in our patient. As a general rule, AMR from preformed isohemagglutinins is only seen in the first 2–3 weeks after transplant and this is why plasmapheresis is employed whenever the titers rise. After this 2- to 3-week period, there exists a phenomenon that has been referred to as "accommodation," where circulating anti-donor antibody is present without evidence of allograft injury [14, 15]. The presence of C4d deposition in the peritubular capillaries without histological evidence of inflammation in the 6-month protocol biopsy of our patient, suggests that the endothelial cells of the graft might have "accommodated" to the patient's microenvironment.

Although ABOi transplantation may be associated with increased perioperative bleeding and infections, the experience detailed in this report highlights that ABOi pediatric kidney transplantation can be safe and efficacious with a simplified pre-conditioning regimen. However, more experience is needed to better delineate this. More importantly, ABOi transplantation can yield options that both shorten waiting times and provide a novel approach to transplanting the ultra-highly sensitized patient, particularly when combined with the use of paired kidney exchange programs. Currently, there is a shortage of organs, with prolonged waiting times, especially for sensitized adults and children. Although the number of patients waiting for a kidney transplant continues to increase, the number of deceased organ donors has remained relatively static for the last 6 years [3]. It is in this context that the consideration of ABOi transplantation with the paired exchange program may provide increased benefits.

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References

1. Meier-Kriesche HU, Scornik JC, Susskind B, Rehman S, Schold JD (2009) A lifetime versus a graft life approach redefines the importance of HLA matching in kidney transplant patients. Transplantation 88:23–29

2. Van Arendonk KJ, Boyarsky BJ, Orandi BJ, James NT, Smith JM, Colombani PM, Segev DL (2014) National trends over 25 years in pediatric kidney transplant outcomes. Pediatrics 133:594–601
3. US Department of Health and Human Services (2009) Overall by organ current US waiting list. In: Administration HRaS. Accessed 22 February 2014
4. Shishido S, Hyodo YY, Aoki Y, Takasu J, Kawamura T, Sakai KK, Aikawa AA, Satou H, Muramatsu MM, Matsui Z (2012) Outcomes of pediatric ABO-incompatible kidney transplantations are equivalent to ABO-compatible controls. Transplant Proc 44:214–216
5. Mamode N, Marks SD (2013) Maximising living donation with paediatric blood-group-incompatible renal transplantation. Pediatr Nephrol 28:1037–1040
6. Lipshutz GS, McGuire S, Zhu Q, Ziman A, Davis R, Goldfinger D, Reed EF, Wilkinson AH, Danovitch GM, Pham PT (2011) ABO blood type-incompatible kidney transplantation and access to organs. Arch Surg 146:453–458
7. Winters JL, Gloor JM, Pineda AA, Stegall MD, Moore SB (2004) Plasma exchange conditioning for ABO-incompatible renal transplantation. J Clin Apher 19:79–85
8. National Kidney Registry http://www.kidneyregistry.org, Accessed 30 June 2014
9. Montgomery RA, Locke JE, King KE, Segev DL, Warren DS, Kraus ES, Cooper M, Simpkins CE, Singer AL, Stewart ZA, Melancon JK, Ratner L, Zachary AA, Haas M (2009) ABO incompatible renal transplantation: a paradigm ready for broad implementation. Transplantation 87:1246–1255
10. Chacko B, Trevillian P (2014) ABO-incompatible paired kidney exchange for failed desensitization. Transplantation 97:e8–e9
11. Ferrari P, Hughes PD, Cohney SJ, Woodroffe C, Fidler S, D'Orsogna L (2013) ABO-incompatible matching significantly enhances transplant rates in kidney paired donation. Transplantation 96:821–826
12. Wiebe C, Gibson IW, Blydt-Hansen TD, Karpinski M, Ho J, Storsley LJ, Goldberg A, Birk PE, Rush DN, Nickerson PW (2012) Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. Am J Transplant 2:1157–1167
13. Willicombe M, Brookes P, Sergeant R, Santos-Nunez E, Steggar C, Galliford J, McLean A, Cook TH, Cairns T, Roufosse C, Taube D (2012) De novo DQ donor-specific antibodies are associated with a significant risk of antibody-mediated rejection and transplant glomerulopathy. Transplantation 94:172–177
14. Haas M (2010) The significance of C4d staining with minimal histologic abnormalities. Curr Opin Organ Transplant 15:21–27
15. Fidler ME, Gloor JM, Lager DJ, Larson TS, Griffin MD, Textor SC, Schwab TR, Prieto M, Nyberg SL, Ishitani MB, Grande JP, Kay PA, Stegall MD (2004) Histologic findings of antibody-mediated rejection in ABO blood-group-incompatible living-donor kidney transplantation. Am J Transplant 4:101–107