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Monozygotic transplantation: Concerns and Opportunities

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Abstract

We describe the case of a 24 year-old female with end stage renal disease from focal segmental glomerulosclerosis (FSGS) diagnosed at age 16, who underwent monozygotic triplet transplantation at age 21 from her sister. Monozygosity was established by buccal smear DNA PCR amplification using short tandem repeat (1) profiling for 16 genetic alleles. All immunosuppression was discontinued by one-month post-transplant. To evaluate the use of immunosuppression in HLA identical monozygotic transplantation, we interrogated the OPTN (Organ Procurement Transplant Network) database for all transplants conducted from 1987–2006. We identified 194 probable identical twin transplantations based on age, gender, race, ethnic category, blood type and HLA match. We evaluated the use of various immunosuppressive agents at discharge, 6-months and 1, 2, and 3 years after transplantation. Seventy one percent of these patients at discharge and 34% at the end of one-year were on immunosuppression. At discharge 61% received steroids and 30% received calcineurin-inhibitors and 66% of these remained on calcineurin-inhibitors at one-year. Renal function was superior among those not maintained on immunosuppression. Thus, monozygotic transplantation confers an immunologic advantage that allows immunosuppression elimination despite a risk of recurrent glomerular disease such as FSGS with appropriate evaluation and management.

Keywords

kidney transplantation; twins; immunosuppression

Introduction

The first successful renal transplant was performed between identical twin siblings, on December 23rd, 1954. The recipient was a 24 year-old man with chronic glomerulonephritis and nephrotic syndrome. Full thickness skin grafts between the twins placed approximately two months prior to the transplant provided evidence of monozygosity and immunologic compatibility. Immunosuppression was not used. The recipient never developed rejection but died 8 years later from recurrent glomerulonephritis (2). The donor eventually developed endstage renal disease (ESRD) from undefined causes and initiated dialysis in November 2007, 53 years after donation (3).

This first living donor transplant emphasizes the greatest potential survival advantage based on lack of immunogenicity and “lowest risk of rejection” permitting avoidance of immunosuppression and its associated adverse effects. It is pertinent that the recipient

developed recurrent disease. Whether immunosuppressive medication would have delayed or prevented the recurrence is unknown. Despite the introduction of potent immunosuppression, the incidence of recurrent disease has remained relatively constant over decades (4–6). With the use of potent immunosuppressants in modern transplantation, “less than ideal” HLA mismatched living and deceased-donor transplants have been very successful (1). These medications, however, result in numerous infectious, malignant, metabolic, cardiovascular and cosmetic adverse effects and may be nephrotoxic (7). Ideally, immunosuppression should be tailored to individual patients based on their risk of rejection, HLA match, side effect profile, age of the recipient etc. Over-immunosuppression negatively affects long-term patient and graft-survival and immunosuppression in general is financially burdensome. Transplantation of monozygotic siblings represents an opportunity for minimal or no immunosuppression.

There is paucity of data and lack of guidelines regarding evaluation of monozygosity between donor and recipient, the level and type of immunosuppression required in HLA identical monozygotic transplantation, and evaluation to prevent recurrent disease. We recently transplanted a monozygotic sibling pair, from monozygous triplets, for a patient with ESRD from focal segmental glomerulosclerosis (FSGS). We believe this is the first report of a triplet monozygotic transplant and describe the evaluation and immunosuppressive regimen we used and the reasons for our choices. We further analyzed the OPTN database to determine the use of immunosuppression in monozygotic transplants and to establish whether there exists an opportunity for immunosuppression minimization or elimination in this unique transplant situation.

Case Report and Methods

Our patient is now a 24 year-old white female diagnosed with biopsy proven FSGS at the age of 16 after developing proteinuria and hematuria discovered on routine urine dipstick. She failed treatment with steroids and progressed to ESRD within 4-years of the primary diagnosis. She initiated hemodialysis at the age of 20. The same year she underwent evaluation for a living related donor (LRD) HLA identical triplet transplant from her sister. Both the recipient and the donor were seronegative for cytomegalovirus (CMV).

Buccal swabs for genetic testing were used to determine monozygosity. Polymerase chain reaction (PCR) was used for DNA amplification. Genetic concordance was established at 16 allelic sites using short tandem repeat profiling (Genelex Corp, Seattle, WA). This has a high specificity with a 1 in 1,780,405 chance that a fraternal twin could have the same DNA profile. To exclude a genetic cause of familial FSGS and assess the donor's risk of developing FSGS, the recipient underwent genetic testing for slit diaphragm protein NPHS2 (podocin) mutation (Athena Diagnostics, Inc., Worcester, MA), which was negative.

The transplant occurred on June 10, 2004. The recipient received methylprednisolone (7 mg/kg) intraoperatively and then oral prednisone for the first 5 days after which it was discontinued. She received low dose mycophenolate mofetil (MMF) (500 mg bid) and tacrolimus (target levels 5–10 ng/mL) initially. MMF was discontinued within a week. Tacrolimus was discontinued after 1 month. No induction therapy was used.

The patient was anuric prior to the transplant. Proteinuria was monitored, daily, in the immediate postoperative period and weekly for the first month, monthly for 1 year post-transplant and every 2–3 months thereafter with random spot urine protein to creatinine ratios (8). She received infection prophylaxis with acyclovir to prevent herpes infection, nystatin to prevent candidiasis and trimethoprim-sulfamethoxazole to prevent bacterial

infection and *Pneumocystis*. All were discontinued by one month post-transplant. She was discharged on postoperative day 3 with a nadir serum creatinine of 0.7 mg/dl.

Her post transplant course was complicated by two episodes of transplant pyelonephritis at months 13 and 18 at which time single strength daily trimethoprim-sulfamethoxazole was re-initiated. Lisinopril was added for mild hypertension. At 3 years post-transplant she maintains excellent graft function with a creatinine of 1.0 mg/dl with proteinuria less than <500 mg/dl. Her triplet donor sister continues to do well with no evidence of proteinuria.

Methods for analysis of UNOS

This study was approved by the Washington University Human Research Protection Organization and the United Network of Organ Sharing (UNOS) and OPTN. We used the OPTN registry from 1987 to 2006 to determine possible donor-recipient paired twins. Twin transplantations were determined by examining living donor recipients and matching the recipients and their donors on the following variables: age, gender, race, ethnic category, blood type and HLA match. The recipient-donor pair must have had the same age, gender, race, ethnicity, and blood type, as well as HLA identity.

Once we determined recipients who were possible twins we examined immunosuppression use in the OPTN registry. We investigated use of cyclosporine (CSA), tacrolimus (TAC), mycophenolate mofetil (MMF), azathioprine (AZA), sirolimus, or corticosteroids at discharge, six months post-transplant, and one, two, and three years post-transplant. In addition to analyzing the immunosuppressants separately, we categorized them into calcineurin-inhibitors (CSA & TAC), antimetabolites (MMF & AZA), as well as any immunosuppressant. We considered a patient to have discontinued an immunosuppressant if there was use of the immunosuppressant at one time-point and no use at the following time-point. Induction use was determined by the immunosuppressant induction indication in the OPTN discharge records.

Statistical Analysis

Kaplan-Meier survival analysis and log-rank tests were used to compare those on or off immunosuppressants at discharge, 6 months post-transplant, and one-year post transplant. Both patient and graft survival were analyzed to three years post transplant.

To evaluate kidney function, mean creatinine levels were calculated for those who received or did not receive maintenance immunosuppression at the time-points, above, using t-tests. All statistical analyses were done using SAS v. 9.1.

Results from OPTN database

We identified 194 probable identical twin transplantations based on age, gender, race, ethnic category, blood type and HLA match using UNOS discharge records. The demographic characteristics are shown in Table 1. The use of various immunosuppressive agents post-transplant tended to decline over time (Table 2). Seventy-one percent of these patients at discharge and 34% at the end of 1-year were on some form of immunosuppression. Thirty percent were on calcineurin inhibitors at discharge, and 21% were on them one year after the transplant. Steroids were the most frequently used agent, with 61% of the patients being discharged on steroids. By one-year post transplant 27% of the patients remained on steroids. By one-year post-transplant, 66% of the patients were not on any immunosuppressant agents. The demographics of patients on or off immunosuppressants at one-year are shown in Table 3. Recipients off immunosuppression tended to be younger, white, have a cold ischemia time less than 12 hours and an unknown CMV serostatus.

The number of patients who discontinued use of an immunosuppressant agent given that they were on the drug at discharge is shown in Table 4. Of the 138 patients on an immunosuppressant agent at discharge, 56 (41%) were discontinued from all immunosuppressant agents by 6-months post transplant. More subjects were withdrawn from antimetabolites post discharge than calcineurin inhibitors, 44% and 24% respectively.

Except for steroids, which were used in 36% of the transplants, very few of the subjects received induction therapy (Table 2). All other induction agents were used in no more than 6% of the subjects.

Patient or graft survival did not differ over time among those who were on or not on immunosuppression at discharge ($p = 0.98$ and 0.54 respectively). For any time point thereafter patient survival was similar for both groups up until five years post transplant, from which time onward those on an immunosuppressant did worse than those not on an immunosuppressant ($p \leq 0.04$). Graft survival was similar between groups at all time points after discharge.

From 6-months onward renal function improved among those not receiving immunosuppression ($p \leq 0.007$) (Table 5). At three-years, the mean serum creatinine level was 1.46 ± 0.96 mg/dL among those receiving immunosuppression and 1.13 ± 0.21 mg/dL among those not receiving immunosuppression ($p = 0.003$).

Discussion

This study is important for several findings. First, this is the first known renal transplant between a monozygotic pair of a triplet birth. Second, the methods we used to determine monozygosity may be used by others. Third, the evaluation and management we used and the analysis of the OPTN database suggest that minimal to no immunosuppression is possible with monozygotic transplantation. Fourth, there exists an under utilized opportunity for immunosuppression avoidance in monozygotic renal transplantation that may result in superior renal function. Finally, this study may be used by others as a guide to management of future monozygotic transplants.

Evaluation for Monozygosity

Human monozygotic twins (i.e. a single zygote which divides into 2 separate embryos with independent development and births) account for 1 in every 250 live births worldwide (9). Monozygotic twins are genetically identical (unless mutations have occurred during in utero development) and are of the same gender. Blood types and genders of newborns, HLA typing, chorionicity evaluated by prenatal ultrasonography and the examinations of the placentas after delivery have been used to determine twin zygoty (10). These methods have shortcomings and are prone to misinterpretations. It is important to note that monozygosity cannot be accurately proven by usual transplant HLA homology since 25% of dizygotic twins share the same transplant HLA haplotypes. More comprehensive HLA testing, as we performed, is customarily used for bone marrow transplantation and can determine monozygosity. Evaluation of genomic DNA extracted from oral epithelial cells via buccal swabs uses PCR amplification techniques to establish allelic concordance between monozygous twins (11–13). PCR based STR profiling, which is the method used on our patient, is a relatively new method of DNA fingerprinting that is cost-effective and accurate (14).

Need for Immunosuppression in HLA identical sibling transplantation

There are no randomized prospective or retrospective data to guide the use and need for induction, steroids, short or long-term maintenance immunosuppression in HLA identical sibling transplantation. There are no randomized studies in the literature that address “tailoring” immunosuppressive therapy based on HLA match. There are only a few case reports that describe monozygotic twin kidney transplants that have successfully been conducted with the use of minimal or no immunosuppression (2,4,9,15). In 2002, this observation was extended to liver transplants, with the first 2 case reports of successful monozygous twin liver transplants being performed without the use of any immunosuppression except intra-operative steroids (16).

A recent study of the USRDS database analyzing 23,443 patients transplanted between 1995 to 2002 revealed a mere 4%–8% lower use of immunosuppression with MMF and tacrolimus at 6 months in the “No HLA ABDR mismatch group” compared to the DR mismatch group, with no difference in the doses of CSA, sirolimus, or AZA between the two groups (17). All patients in the “No mismatch group” were on some form of immunosuppression with approximately 80% on a combination of an antimetabolite and calcineurin inhibitor, exposing them to potential nephrotoxicity. Gerrits, et al, recently demonstrated that decreasing the dose of AZA after 2 years of transplantation in HLA-identical allograft recipients did not result in any clinical episodes of rejection when followed for 1-year (18). In addition, no increase in the T cell reactivity markers, such as IL-13 and IF-gamma in the recipient peripheral blood mononuclear cells was found. The use of immunosuppression in monozygotic twins was not assessed.

Our analysis of the OPTN database showed that 71% of twin transplants were discharged on immunosuppression and 33% still remained on some form of immunosuppression at 3-years after transplantation and 13% were on triple therapy at 3-years after transplantation.

Use Of Steroids In HLA Matched Monozygotic Transplants

We administered a brief course of steroids, a calcineurin inhibitor and an antimetabolite in our monozygotic twin recipient. The reason for this is that the mechanism of rejection of an allograft is not solely based on alloantigen recognition, but also on other factors that increase immune responsiveness and therefore, the risk of rejection. Trauma and ischemic damage to the tissues during surgery release cytokines and other endogenous “alarm or danger signals” that can activate the immune cascade despite complete HLA homology between the donor and recipient (19). In addition, oxidative and ischemia-reperfusion injury associated with surgery may modify donor DNA and has the potential to alter gene expression post-transplantation. These “epigenetic modifications” can predispose to allograft rejection, increase risk of malignancy and cause other deleterious effects. Such changes to donor DNA may become stable and heritable with important implications for transplant outcomes (20). Significant discordance in the donor and recipient may be observed with exposure to toxins, bacteria and viruses and epigenetic modifications that can alter immunogenicity and induce autoreactivity. The importance of environmental influences and epigenetic modifications is demonstrated by marked phenotypic differences in disease manifestation, response to treatment and recurrence of disease in monozygotic twins despite genetic concordance (21). The use of steroids in the perioperative period can block immune responses at various levels induced by these alternate mechanisms of immune reactivity and reduce the risk of acute rejection.

Should HLA matched living donor transplants be allowed in FSGS?

Focal segmental glomerulosclerosis is the most common primary glomerular disease resulting in ESRD affecting a wide range of age groups and ethnicities, with the highest incidence in the African American population (22,23). Presently, FSGS is the most common primary glomerular cause of ESRD in renal transplant recipients (24,25). Primary FSGS has a high risk of recurrence after kidney transplantation with a rate of 30–50% and portends a poor prognosis for graft survival. The average time to recurrence is 1.3 years (range 5 days to 6 years) (16). The relative risk of graft failure with post-transplant FSGS is 2.25, with a 5 year renal allograft survival rate of 34.2% (26,27).

The risk of recurrence is highest in patients younger than 20 years at the time of primary diagnosis, Caucasian recipient-race, African American donors, those with a rapidly deteriorating course leading to ESRD within 3 years of diagnosis, history of recurrence in a prior allograft and histological severity (mesangial hypercellularity on native kidney biopsy) (28–31). African American recipients have lower rates of recurrence (32,33).

Genetic or acquired mutations (familial or sporadic) in genes encoding the slit diaphragm proteins- podocin (NPHS2), nephrin (NPHS1), α -actinin 4, CD2AP and TRPC6 have been reported in 15% of patients with primary FSGS (34,35). The most common type of familial FSGS is from mutations in the NPHS2 (podocin) gene (36). Homozygous and compound heterozygous mutations in NPHS2 tend to present early in life and cause steroid resistant nephrotic syndrome with low (<10%) but definite risk of post transplant recurrence (36,37). Although there was no history of FSGS in our patient's family, we excluded one possible genetic cause since the donor was a monozygotic triplet. Commercial testing for only NPHS2 (podocin) is available and helped assess the donor's risk of developing FSGS. As the human genome becomes better defined we anticipate that the transplant community will be able to predict a donor's risk of developing ESRD better.

Since the risk of acute rejection is low, recurrence of primary glomerulonephritis is a relatively more common cause of graft loss in HLA identical living donor transplants (38). Among all transplants, recurrent glomerulonephritis is the third most common cause of graft loss, preceded by death with a functioning graft and chronic rejection (27). Earlier small studies recommended that HLA-matched and living donor transplants should be avoided in patients with FSGS due to a higher risk of recurrence and graft loss compared to deceased-donor transplants and living donor transplants in non FSGS patients (30,39,40). More recent, larger studies, however, suggest improved outcomes and a survival advantage with living donor transplants in FSGS (26,27,33,41). In 2003, Cibrik et al reported the results of a large study using the USRDS and the US Scientific Renal Transplant Registry (SRTR) data base and found that HLA matched living donor transplants in patients with FSGS had a better annual death-censored graft survival rate than 6 antigen matched cadaveric or unmatched living/cadaveric transplants (41). This supports matched living transplantation in FSGS. The rate of recurrence of FSGS was not assessed. African Americans particularly benefit from a living related donor transplant given their lower risk of recurrence (33).

Limitations

The major limitation is in the certainty of determination of monozygosity in the registry data. Twin transplantations were determined by examining living donor recipients and matching the recipients and their donors on age, gender, race, ethnic category, blood type and HLA match. Based on these parameters we estimated the possibility of non-monozygosity. The simplest estimate of fraternal twins could be based on the following probabilities: 0.25 for each of the four ABO blood types x 0.50 for each of two genders x 0.25 for HLA identity = 3%. The ABO blood groups are not distributed equally. The

probability of ABO identity would be between 0.5 and 1 and we estimated the probability to be 0.75. This would give an estimate of $0.75 \times 0.5 \times 0.25 = 9\%$. For every 100 identical twin pairs, however, there are approximately 200 fraternal twin pairs, and the number of those fraternal twins who will look “identical” by gender, HLA, and ABO combined is then $200 \times 0.73 \times 0.5 \times 0.25 = 18.75$. This yields 100 true identical and 18.75 pseudo-monozygotic twins, so the chance of pseudo-monozygotes in the OPTN data base is $18.75/(100 + 18.75) = 16\%$.

It is unlikely, however, that STR DNA analyses have been used historically to determine monozygosity. There were no differences in the use or non use of immunosuppression based on the year of transplant so we do not believe the recent availability of STR analyses could bias the findings. We recommend that STR DNA analyses be performed pretransplant to determine monozygosity. Based on our calculations a “twin” transplant of the same gender, same ABO blood type, and same HLA has an 84% chance of being an identical twin. We believe that the 16% chance is too high to risk withdrawal of immunosuppression and monozygosity should be determined using the most modern techniques. The methodology we used to determine probable monozygotic twins in the OPTN database might be useful for clinicians where STR analyses are not available or for clinicians approached by post transplant twin recipients who wish to discontinue immunosuppression when the donor is not available.

In conclusion, we describe a unique case of monozygotic triplet kidney transplant in a patient with focal segmental glomerulosclerosis. This case demonstrates the excellent graft survival and low risk of rejection that is seen in homotransplants even in the absence of immunosuppressive therapy. Our case and, analysis of the OPTN database and review of the literature, suggest that most centers avail themselves of the opportunity for immunosuppression minimization or elimination among these transplants. However, for many, there exists a missed opportunity for immunosuppressive minimization in well HLA-matched patients, especially in monozygotic twin transplantation that may allow for better graft function and survival. Because of the potential of immune system activation from surgical tissue damage at the time of transplantation and the possibility of heterologous immunity, we recommend high dose perioperative steroids, followed by a rapid taper to avoid the short and long-term consequences of immunosuppression. At our institution, we encourage the use of HLA-matched living donors in patients with FSGS, but it is important for the donor and recipient to understand the risk of recurrence.

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