

Short Original

Kidney transplant from a monozygotic twin living donor with no maintenance immunosuppression[☆]

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ABSTRACT

Standard immunosuppression is used in about 60% of patients receiving kidney grafts from their monozygotic twins living donor although an alloimmune response can not take place. The aim of the study was to assess the clinical response in patients receiving renal grafts from a monozygotic twin living donor when no immunosuppressive therapy is used.

Methods: This is a retrospective observational study of patients receiving kidney grafts from their monozygotic twins from 1969 to 2013. The following data were recorded: age, renal graft recipient's primary disease, renal function, renal survival and overall survival. Immunosuppressive therapy included a single intraoperative dose of methylprednisolone 500 mg and no maintenance immunosuppression.

Results: Five patients with kidney grafts from their monozygotic twins were identified in our centre. Mean age at transplantation was 33 years (27-39). One-year overall survival and graft survival were 100%. Mean creatinine level was 0.96 ± 0.2 one year after transplantation, and 1.2 ± 0.37 mg/dl at most recent follow-up. Two patients died with a functional graft more than 15 years after kidney transplantation (causes were melanoma and cardiovascular event respectively). Follow-up was lost in a patient one year after transplantation. Two patients are alive with a functioning graft at 18 months and 42.5 years after transplantation respectively.

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Conclusion: Kidney transplantation from a monozygotic twin living donor is associated with excellent clinical outcomes. Immunosuppressive therapy to suppress alloimmune response is probably unnecessary if zygosity has been confirmed.

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Trasplante renal de donante vivo entre gemelos monocigotos sin inmunosupresión de mantenimiento

R E S U M E N

Palabras clave:

Trasplante renal de donante vivo
Inmunosupresión
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Los pacientes trasplantados de riñón de gemelo monocigótico reciben en un 60% de los casos algún tipo de inmunosupresión estándar a pesar de la imposibilidad teórica para generar una respuesta aloimmune. El objetivo de este estudio es evaluar la respuesta clínica de los receptores renales de donante vivo de gemelo monocigoto sin tratamiento inmunosupresor. **Método:** Estudio observacional retrospectivo entre 1969 y 2013 de pacientes trasplantados renales de donante vivo entre gemelos monocigotos. Se ha recogido edad y enfermedad primaria del receptor, función renal, supervivencia renal y global. El protocolo inmunosupresor consistía en la administración de una dosis única intraoperatoria de 500 mg de metilprednisolona sin otra inmunosupresión de mantenimiento.

Resultados: Se identificó a 5 receptores renales de gemelos idénticos en nuestro centro. Edad media en el momento del trasplante 33 años (27-39). La supervivencia a un año de los pacientes y el injerto fue del 100%. La creatinina media al año fue de $0,96 \pm 0,2$ y al último seguimiento de $1,2 \pm 0,37$ mg/dl. Dos pacientes fallecieron con injerto funcional más de 15 años después del trasplante (uno debido a melanoma y otro debido a un evento cardiovascular). Se perdió el seguimiento de un paciente al año del trasplante. Los 2 pacientes restantes están vivos 18 meses y 42,5 años después del trasplante, respectivamente, con injerto funcional.

Conclusión: El trasplante renal entre gemelos monocigotos ofrece excelentes resultados clínicos. Probablemente el tratamiento inmunosupresor para inhibir la respuesta aloimmune es innecesario en estos casos cuando se haya comprobado la cigosidad.

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Introduction

Renal transplant from a living monozygotic twin donor, though uncommon, may be considered the ideal renal transplant procedure, given the good renal and overall survival rates it offers. It also offers the opportunity to minimise or stop immunosuppressive therapy.

In 1954, Murray et al. carried out the first successful renal transplant between monozygotic twins without immunosuppressive therapy.¹ Following the success of that transplant, in the 1950s and 1960s, various case series were described throughout the world with good renal survival.²⁻⁵ Subsequently, with the advent of modern immunosuppression in the 1970s, in order to avoid acute rejection and primary disease recurrence, patients with a transplant from a monozygotic twin donor started to receive maintenance immunosuppressive therapy, despite the supposed absence of alloimmune response due to being monozygotic twins.^{6,7} Currently, there are no randomised studies or clinical

guidelines that evaluate what type or dose of immunosuppression should be given in renal transplants from monozygotic twins. There are reviews recommending the use of single-dose methylprednisolone and the use of other immunosuppressors for a short period.⁸ There are also case series of renal transplants between monozygotic twins that minimised, or did not give, immunosuppressive therapy, with good renal outcome.⁹⁻¹²

To assess the need to administer or to stop maintenance immunosuppressive therapy, it has been proposed that patients undergoing this type of transplant have zygosity analysis using DNA analysis to establish the differences between monozygotic twins (those that share 100% of their genetic material) and dizygotic twins (those that share approximately 50% of their genetic material).¹³

The aim of this study was to evaluate the clinical response of recipients of renal transplants from living monozygotic twin donors, in transplants performed at our centre without maintenance immunosuppressive therapy.

Methods

This was an observational retrospective study of living donor renal transplants between monozygotic twins performed in the Nephrology Department of *Hospital Clínic de Barcelona*, between 1969 (the first renal transplant performed in the hospital) and 2013.

We identified 5 patients who had a renal transplant from a living monozygotic twin donor. Clinical and analytical data were collected at one year post-transplant and at most recent follow-up. Monozygosity was not analysed with DNA techniques, zygosity being assumed from HLA typing.

The 5 patients received a single dose of 500 mg of methylprednisolone in the operating theatre as immunosuppressive therapy. No other immunosuppressive treatment was started. The patients did not receive prophylaxis against cytomegalovirus.

Results

The mean age of the 5 recipients of renal transplant from an identical twin was 27 years (range 20–39 years) at the time of transplant. All patients shared blood group and 6 HLA identities with their donors. One patient had previously received a transplant. The cause of end stage renal disease was not identified in 3 patients. One patient had membranoproliferative glomerulonephritis and one patient (previously transplanted) had interstitial nephropathy.

Patient survival and graft survival at 1 year were 100%. Mean creatinine at 1 year was 0.96 ± 0.2 mg/dL. At 5 years, both patient survival and renal survival were 100%. Mean creatinine was 1.2 ± 0.37 mg/dL. One patient died with a functional graft (last creatinine 0.8 mg/dL) 16 years after the transplant, due to malignant melanoma with multi-organ metastases, aged 41 years. Another patient died aged 65 years due to a cardiovascular event, 22.5 years after transplant (last creatinine 1.5 mg/dL). One patient was lost to follow-up at 1 year with a functioning graft and creatinine of 1.2 mg/dL. The 2

remaining patients were still alive at 18 months and 42.5 years post-transplant, with functioning kidneys and serum creatinine of 1.2 mg/dL and 1.1 mg/dL, respectively (Table 1). The last transplant patient had protocol biopsies at 3 months and 1 year, with no signs of cellular or humoral rejection. The other patients did not have a biopsy because they had normal renal function and protocol biopsies were not done at that time. None of the 5 patients has had clinical acute rejection and they have not received any further immunosuppressive therapy during their follow-up.

Discussion

Our series of 5 cases of renal transplant between monozygotic twins treated with intra-operative single-dose methylprednisolone with no maintenance immunosuppression shows good renal and overall survival without risk of developing acute rejection or chronic humoral rejection.

Living donor transplantation represents a way to increase preventative renal transplants and transplants for patients on the waiting list, as it offers better renal survival and quality of life, and is a cost-effective treatment.¹⁴ Currently, living donor renal transplant makes up around 50% of all renal transplants in some countries, and this percentage is increasing in countries such as Spain, which previously were performing mainly cadaveric donor transplants.¹⁵

Various studies have shown that donation between monozygotic twins is the best treatment option with excellent renal and overall survival, but there is disagreement regarding the immunosuppressive therapy they should receive.^{6,12} Kessaris et al. showed that in the United Kingdom more than 50%, and in the USA more than 2 thirds of patients with a renal transplant from their identical twin were receiving long-term immunosuppressive therapy.⁶ The authors explained that in some patients, immunosuppression was given to prevent primary disease recurrence, despite the majority of patients not having a primary renal disease at risk of recurrence. In the survival analysis, patients with a theoretically elevated risk of recurrence who did not receive immunosuppressive therapy,

Table 1 – Population characteristics.

Year of transplant	Age at RT	Primary renal disease	Creatinine at 1 year (mg/dL)	Proteinuria at 1 year (mg/24 h)	Creatinine at last follow-up	Proteinuria at last follow-up (mg/24 h)	Current status 2014
1969	30	Unknown origin	0.8	131	1.1	121	Functioning graft
1975	20	Unknown origin	1.5	102	1.5	130	Died (22.5 years post-RT with functioning graft)
1977	25	MPGN	1	255	0.8	247	Died (16 years post-RT with functioning graft)
1981	23	Unknown origin	1.1	78	1.2	103	Follow-up in different centre (functioning graft)
2011	39	Interstitial	1.3	230	1.2	126	Functioning graft

MPGN: membranoproliferative glomerulonephritis; RT: renal transplant.

had no increased risk of primary disease recurrence. In the review by Krishnan et al. of the Organ Procurement Transplant Network database from 1987 to 2006, it was shown that 71% of patients with a transplant from an identical twin stopped immunosuppressive therapy at 1 year, 33% continued with some type of immunosuppression, and 13% continued with standard triple therapy. In the survival analysis the group that stopped immunosuppression had better renal survival at 1 year.¹²

Given the results obtained by other groups and our results, it seems reasonable to propose reducing immunosuppression to the absolute minimum in living donor renal transplants between identical twins. In the ideal situation of monozygotic twins, we propose giving an intra-operative single dose of steroids with the aim of preventing ischaemia–reperfusion damage. Damage from ischaemia–reperfusion during surgery activates various cytokines that can activate the immune response despite complete HLA identity between the donor and recipient. It has also been described that ischaemia can modify donor DNA and genetic expression post-transplant.¹⁶ Therefore, we suggest the use of intra-operative steroids to block the immune response at several levels and reduce the risk of acute rejection. The potential benefits of subsequent immunosuppressive therapy should be carefully evaluated in patients with risk of primary disease recurrence, because immunosuppressive therapy, particularly with steroids and calcineurin inhibitors, is associated with serious infectious, cardiovascular, and oncological complications, as well as the deleterious effect of calcineurin inhibitors on the graft.^{17,18} In our series, we emphasise that we have observed no acute or chronic rejection as a long-term cause of graft loss with the proposed immunosuppression model, but there was 1 case of neoplasia, despite not being on immunosuppressive therapy. We think that this neoplasm, 16 years post-transplant, was unrelated to the transplant, as the incidence of this type of tumour is one of the most increasing in Spain.¹⁹

DNA analysis has been used, historically, to determine monozygosity.^{20,21} Nowadays, monozygosity tests using DNA analysis are available and can be used to assess the need for immunosuppressive therapy and prevent graft rejection, or when there is a high risk of primary disease recurrence. Krishnan et al. recommended pretransplant monozygosity analysis using DNA in saliva.¹² A recent review proposed always performing zygosity studies in twins, since 25% of dizygotic twins can have complete HLA identity and so would falsely be presumed monozygotic.²² The authors proposed multilocus testing (analysing various loci from different chromosomes) to identify a series of DNA fragments that are present in all individuals, but which are highly variable, and which would allow identification of monozygotic twins. This technique is known as multilocus DNA fingerprinting.

The greatest limitation of our series was that we did not determine monozygosity between donors and recipients; we simply analysed the blood group and HLA identities, estimating the possibility of monozygosity, because in the transplants performed before 2000, possible genetic variability was not taken into account, and in the last transplant, the DNA fingerprinting technique was not routinely performed in our laboratory.

In summary, living donor renal transplant between monozygotic twins, though uncommon, can be considered the ideal renal transplant, as it does not require maintenance immunosuppressive therapy. Due to potential immune-system activation, we recommend an intra-operative single dose of steroids to prevent acute rejection, once monozygosity has been demonstrated.

Conflicts of interest

The authors declare no conflicts of interest.

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