Pediatric renal transplantation: A single center experience over 14 years

Delucchi A, Ferrario M, Varela M, Cano F, Rodriguez E, Guerrero JL, Lillo AM, Wolff E, Godoy J, Buckel E, Gonzalez G, Rodriguez J, Cavada G. Pediatric renal transplantation: A single center experience over 14 years.

Abstract: Between 1989 and 2003, 100 transplants were performed in 96 patients at the pediatric nephrology unit of the Calvo Mackenna Children's Hospital. Mean age 10.9 ± 3.9 yr (1–17.6), 30% from LD. Donors were younger than 5 yr in five patients and all recipients received an '*en bloc*' graft. Original disease was hypo/dysplasia 27%, reflux nephropathy 22 and 17% chronic glomerulonephritis. The immunosuppressive protocol during the first period (n = 56, 1989–2000): Cyclosporine, steroids and azathioprine, and during the second period (n = 44, 2001–2003): FK, steroids, MMF and anti-CD25 antibody (mAbs). AR was reported in 22 patients, 11% in LD, 31% in DD ($p < 0.01$). The AR rate decreased from 40 to 8% after anti-CD25 monoclonal induction. Patient actuarial survival rate at 1, 3 and 5 yr was 100% for LD and 96% for DD. The overall actuarial graft survival at 1,3, and 5 yr was 96.7, 96.7 and 71% for LD and 89, 76 and 73% for DD donors. Graft survival rate improved from the first period (1989–2000) to the second period (2001–2003; $p = 0.05$). No difference in graft survival rate with HLA-A,B,DR matching was found. Graft survival rate was better when cold ischemia time was <24 h ($p < 0.01$). CMV infections increased from 19 to 40% when MMF and anti-CD25 Ab were introduced ($p < 0.01$). The height/age *Z* score at 1, 3 and 5 yr post-transplant was −2.2, −2.1, −2.2, respectively, for children older than 7 yr and −1.8, −1.9, −2.1 for those transplanted younger than 7 yr of age who were switched to alternate day steroids ($p < 0.01$). The cause of graft lost was: chronic rejection eight, non-adherence four, AR four and vascular thrombosis two. The cause of death in two patients was fungus septicemia and accelerated rejection. Pediatric renal transplantation can be performed in our group with acceptable morbidity, low mortality and graft survival rates similar to other reports in North America and Western Europe. Graft survival rate improved with newer immunosuppression and greater experience at the center. Management of non-adherence and chronic rejection remain the major challenges.

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Abbreviations: Ab, antibody; AR, acute rejection; ATN, acute tubular necrosis; CMV, citomegalovirus; CRF, chronic renal failure; CsA, cyclosporin A; DD, deceased donor; ESRD, end-stage renal disease; FK, tacrolimus; FSGS, focal segmental glomerulosclerosis; GDP, gross domestic product; HLA, human leucocyte antigen; LD, living donor; mAbs, monoclonal antibodies; MMF, mycophenolate mofetil; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; rhGH, received growth hormone.

Renal transplantation is the treatment of choice in pediatric patients with CRF, based on the quality of life improvement and in the rehabilitation obtained (1–3). Recently, patient and graft survival rates have significatively improved, because of technological advances and to the introduction of new immunosuppressive drugs (4, 5). Pediatric registries are essential for promoting health policies and achieving successful renal transplantations. Chile, with a population

of 15 million has a per capita GDP of $4,212.86 and an adult literacy rate of 92%. Life expectancy at birth is 75.9 yr and the child mortality rate is 7.8%. The incidence of ESRD is 8.4/million of children < 18 yr of age. Analysis of the Public Health Institute of Chile database demonstrated that, in 2003, the incidence of transplantation was 17/million inhabitants, ca. 300 renal transplants are performed yearly and pediatric recipients accounted for 15% (Annual Report of Transplant Corporation in Chile, unpublished data). This number will undoubtedly increase with medical progress; therefore, it is a pediatric challenge to create a good multidisciplinary team to achieve successful renal transplantations. In 2003, the Chilean Ministry of Health increased the funds assigned to renal transplantation to $US 10 000/patient/yr in order to promote and support new strategies in immunosuppressive therapy, which will improve outcomes in children. With this aim, we started, in our center, a registry to obtain a transplantation follow-up status, which represents 50% of the children receiving a renal allograft in Chile in public hospitals.

This report summarizes data between 1989 and 2003, which includes children younger than 18 yr at the time of transplant.

Patients and methods

Between 1989 and 2003, 100 kidney transplants in 96 patients, 56 male, were performed at our center; 30 of them from LD, four were second transplants and 12 of them were preemptive. The mean age was 10 ± 3.9 yr (1–17.6). In five patients, the donor was younger than 5 yr and five patients received an '*en bloc*' graft. The original disease leading to CRF was hypo/dysplasia (27%), reflux nephropathy (22%) and chronic glomerulonephritis (17%). General patient characteristics are shown in Table 1.

The immunosuppressive protocol was changed during the time span of this report: the first period included (1989–2000) cyclosporine, steroids and azathioprine, and the second period (2001–2003) cyclosporine or FK, steroids, MMF and anti-CD25 antibody (Fig. 1). IL-2 receptor blocker, Simulect®, was employed in two doses, one at the time of transplant and the second dose was administered at day 4 after transplant. The incidence of transplantation increased every year, not only due to the number of transplants performed, which showed an increase from 3 to 20 new cases per year but also the proportion of younger recipients increased. Our exclusion criteria included: donors older than 65 yr old, cold ischemia time > 30 h or significant damage of the kidney during the procurement procedure. Surgical procedures were similar in both study periods. An extraperitoneal approach was utilized in patients weighing > 15 kg, and the intraperitoneal approach for smaller patients. The external iliac vassels were normally used for anastomosis except in patients with an intraperitoneal approach where the aorta and vena cava were used. Uretheral–bladder anastomoses were done using the Gregoire procedure and Foley catheters were maintained for 3 days, except in patients with prior bladder disease.

Table 1. Transplant recipient characteristics

	Percent
Gender	
Male	56
Female	44
Age (yr)	
0–1	2
2–5	12
6–12	54
>12	32
Primary diagnosis	
Congenital hypo/dysplasia	27
Reflux nephropathy	22
Chronic glomerunephritis	17
Others	34
Prior transplant therapies	
Preemptive	12
Hemodialysis	35
Peritoneodialysis	53
Hemo and peritoneodialysis	10

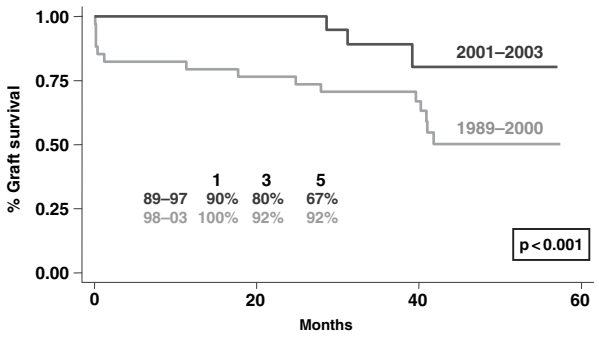

Fig. 1. Percent graft survival by period of transplant.

Information on renal transplants was collected with a common template, including three items: demographics (gender, age, original disease leading to CRF and type of dialysis), transplantation characteristics (donor source, cold ischemia time, HLA type of recipient and donor, immunosuppressive therapy, AR, graft function, complications, mortality, graft and patient survival) and growth rate from birth, the beginning of dialysis, at the time of transplantation and during the post-transplantation follow-up period.

Statistical analysis

Continuous variables were expressed as mean ± s.d. and growth as height/age *Z*-score. Data were organized to provide analyses of graft survival and the relationship of these end points to variables such as graft source, degree of HLA mismatch, and graft function. Student's *t*-test was applied to compare continuous variables. A Cox proportional hazard model was applied to evaluate the relative risk of graft failure or death of the patient. Chi-square and Fisher exact tests were used to determinate the association between ordinary and nominal variables. Rejection episodes were related to LD or DD and were analyzed with the chi-square Pearson's test. Graft and patient survival rate were

estimated by the Kaplan–Meier curves and compared by log-rank test. $p < 0.05$ was considered significant. Statistical analysis was performed using STATA version 7.0.

Results

The rate of renal transplantation at our center has increased dramatically since 2000 primarily because of the influence of several key factors: the availability of new, young transplant surgeons the initiation of a program of organ procurement embedded in a national program and the transplant team is reinforced, with increased funding assigned to pediatric renal transplantation in order to promote and support new strategies of immunosuppressive therapies.

The number of DD accounted for 50% of the allografts during the first period and 63% in the second period. Thirty percent of patients were switched to alternate day prednisone therapy after the first year post-transplant, if no AR episode occurred. A first AR episode was reported in 22 patients, 11% LD and 31% DD recipients ($p < 0.01$); AR rate decreased from 40 to 8% after anti-CD25 Ab induction was initiated. The incidence of AR increased from 35 to 62% when ATN was present ($p < 0.01$). Delay in the graft function was found in 17% requiring dialysis and graft survival was significantly worse in both donors source groups ($p < 0.005$). The average cold ischemia time was 22 ± 7 h; graft survival was better when cold ischemia time was < 24 h ($p < 0.01$). CMV infection increased from 19 to 40% in the second period when anti-CD25 Ab and MMF were used ($p < 001$). Mean serum creatinine (mg/dl) at 1, 3 and 5 yr post-transplant was 1.0 ± 0.6, 1.3 ± 0.6, and 1.3 ± 0.7. Actuarial graft survival rate was significantly better with a serum creatinine ≤ 1 mg% at 1 yr post-transplant vs. serum creatinine ≥ 1 mg% ($p < 0.05$).

Patient and graft survival

Patient actuarial survival rate at 1, 3 and 5 yr was 100% for LD and 96% for DD recipients. Graft survival rate at 1, 3, 5 yr was 96.7%, 96.7%, and 71% for LD and 89, 76 and 73% for DD. The graft survival rate at 1, 3 and 5 yr in the first period was 90, 80 and 67% and then increased to 100, 92 and 92% in the second period ($p = 0.01$). No significant difference in graft survival rate was found related to variables such as donor source and mismatch for HLA-A, B and DR. In multivariate analysis, presence of ATN ($p < 0.01$), cold ischemia time over 24 h ($p < 0.04$), no induction Ab therapy ($p < 0.02$) and AR ($p < 0.001$) were associated with a significant increased risk of graft failure. Only two patients required anti-hypertensive therapy in this trial; therefore, the incidence and effect of post-transplant hypertension on graft survival was not significant. Cardiovascular complications did not arise and two patients who received FK were switched to cyclosporine as the result of hyperglycemia. At the time of this report 89% of recipients had a functioning allograft with normal renal function in 50%, 9% were on dialysis therapy and 2% had died.

Surgical and medical complications

Infectious complications included urinary tract infections in 20 patients; these being recurrent in more than half the cases, CMV infection in 16 patients and fungus septicemia in one recipient. Non-infectious complications included recurrence of FSGS in two patients, both of whom responded to plasmapheresis and high-dose cyclosporine and vascular thrombosis in two who lost their graft. Only one malignancy occurred: a gastric lymphoma that was detected at the 7th year of follow-up and treated by partial gastrectomy, without losing the graft. Early surgical complications were: hemoperitoneum two, renal disruption two, one associated with arterial hypertension and both cases associated with AR. Late complications: uroperitoneum two, urinoma one, urinary fistula one, lymphocele two, and one patient presented with renal artery stenosis which required angioplasty. The main causes of graft lost were: chronic rejection eight, non-adherence four, AR four and vascular thrombosis two. The cause of death in two patients was fungal septicemia and accelerated rejection respectively.

Growth

The growth rate declined from -0.8 at birth to -1.4 at the beginning of dialysis and to -2.3 at transplantation ($p < 0.05$).The height/age *Z*-score at 1, 3 and 5 yr post-transplantation was -2.25, -2.24 and -2.5. The height/age *Z*-score at 1, 3 and 5 yr post-transplant was -2.2, -2.1, -2.2 for children older than 7 yr and -1.8, -1.9, -2.1 for those transplanted younger than 7 yr of age who had been switched to alternate day steroids ($p < 0.01$). No significant post-transplantation outcome difference in *Z*-score between patients younger and older than 7 yr of age on daily steroid therapy was seen. No patient rhGH.

Discussion

The experience presented during 14 yr of follow-up showed that graft survival rate of 100

allografts at 1, 3 and 5 yr was 96.7%, 96.7% and 71% for LD and 89%, 76% and 73% for DD recipients, being similar at 5 yr post-transplant for both donor sources. When the first 56 transplants were compared with the subsequent 44 transplants, there was an improved graft survival rate of 12% after 3 yr and 25% at 5 yr post-transplant, suggesting a beneficial effect because of new immunosuppression drugs and greater center experience (6). These results were similar to the recent NAPRTCS report (5). Delay in graft function resulted in a lower 5-yr graft survival rate in both donor source groups ($p < 0.005$). One of the most valuable indicators to evaluate following renal substitution therapy in uremic children is growth. The fall a height/age *Z*-score from −0.8 at birth to −1.4 at the beginning of dialysis and to −2.3 at transplantation reflects the impact of uremia on growth failure. After transplantation the height/age *Z*-score at 1, 3 and 5 yr was −2.1, −2.4, −2.5. A statistically significant better growth rate in patients transplanted before 7 yr of age with alternate day of prednisone therapy was found compared with patients older than 7 yr. Multiple trials have been done looking at withdrawing or avoiding steroids. The administration of alternate day steroid dosing has shown a better outcome of height in the prepuberty pediatric population (2, 3), but it has been difficult to use this method because of reduced adherence (4). Depending on the type of immunosuppression and the time of steroid withdrawal, steroids had to be reintroduced in > 50% of the cases after AR episodes. The NAPRTCS described that, in patients transplanted before 5 yr of age, it was possible to observe an accelerated growth or catch-up growth; however, these results were not possible to compare with ours, because an indeterminate number of patients from the NAPRTCS report were treated with rhGH while none of our cases of growth delay received rhGH. This drug is not available in our country because of the high cost involved. This finding allows us to conclude that in order to diminish lost growth potential, transplants should be performed before puberty and in stable patients early steroid withdrawal or steroid free protocols should be used (7, 8). Graft survival rates were significantly worse in the presence of ATN, cold ischemia time over 24 h, no induction antibody therapy and AR episodes. In multivariate analysis, proportional hazards models have been described which suggest that cold storage time over 24 h, ATN, no induction antibody administration and AR are significant contributors to the risk of graft failure. Preemptive transplantation was performed in 12.5% of our patients. In the NAPRTCS report, preemptive modality accounts for 25% of all transplants; recently publications show that this modality seems to be the best for the long-term graft survival (9). Rejection decreased after anti-CD25 mAbs introduction. In our study a 23% AR rate during the first year post-transplantation was detected, irrespective of donor source; most of the episodes were reversed with the use of methylprednisolone. The importance of the opportune diagnosis and treatment of the AR episodes and specially prevention, was demonstrated by the impact of AR on the long-term graft survival (10–12). The most common bacterial infection in pediatric renal transplant recipients was a urinary tract infection during the first month post-transplant and frequently it was associated with bacteremia. The incidence varies between 5 and 36% in different series (13), in our patients, it occurred in 20% of the patients, and in more than half of the cases it was recurrent. CMV was the most frequent opportunistic pathogen. Currently our immunosuppressive protocol does not include anti-CMV prophylaxis, and we are only monitoring CMV (pp65). CMV infection was diagnosed independent of clinical symptoms, when more than 10 nucleuses from 400.000 cells had positive antigenemia. The increase in CMV infections after anti-CD25 Ab induction and MMF treatment did not translate into an increase in the seriousness of infection because the diagnosis of CMV infection was only made by rise in the CMV titers with a good intravenous ganciclovir response was obtained without graft loss (14, 15). The increase in CMV infection incidence should dictate anti-CMV prophylaxis, in our protocol. Other causes of graft loss were renal vessel thrombosis and non- adherence; both a greater risk in the pediatric population. Vascular thrombosis is a devastating complication with an incidence between 0.5 and 6.2% in different series (16), which account for 30 to 50% of early graft lost. In our experience, it represents 2% of the graft losses, whereas in the NAPRTCS report, vascular thrombosis occurred in 12.8% of the graft failures (17).

Finally, it is necessary to consider that non-adherence with immunosuppressive therapy, although frequent in all ages, seems to be greater in the pediatric age group. In our group 13% of the grafts were lost because of this cause; in the NAPRTCS report, it was 4.4%. Other studies (18) show a lack of adherence to the therapy between 30 and 60% being highest in the adolescent age group (19).

In summary, this report confirms that pediatric renal transplantation can be performed in Chile with acceptable morbidity, low mortality and graft survival rates similar to other countries. In our children growth retardation is one of the onerous clinical facets of CRF, independent of allograft source and transplant age; catch-up growth does not occur.

In order to diminish growth potential lost, transplantation should be performed before puberty and in stable patients, early steroid withdrawal or steroid avoidance protocols must be started to achieve catch-up growth. Management of non-compliance and chronic rejection are the major challenges. Prevention of graft dysfunction seems to be possible with the optimal use of newer immunosuppressive drugs.

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