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Low-dose cyclosporin A therapy in cadaver renal transplantation in children

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Abstract. Fifty-one pediatric patients undergoing a first cadaveric kidney transplantation were followed for at least 2 years after grafting. They were divided into two groups: those treated with methylprednisolone plus azathioprine (AZA) and those treated with methylprednisolone plus low-dose cyclosporin A (CyA; median dose 109 mg/m^2 per day ≙ 3.4 mg/kg per day after 1 year). The steroid dosage given was significantly lower in the second group. The 4-year graft survival rate was 68% for the AZA group and 78% for the CyA group. Renal function did not differ significantly in the two groups; after 1, 2, and 3 years, the median 24-h creatinine clearance was 79, 69, and 51 ml/min/1.73 m^2, respectively, for the AZA group and 78, 63, and 68 ml/min/1.73 m^2, respectively, for the CyA group. Linear growth was similar in the two groups. We conclude that in pediatric patients the results of low-dose CyA immunosuppression do not differ significantly from those obtained with AZA in terms of graft survival, renal function, or growth.

Key words: Pediatric renal transplantation - Cyclosporin, low-dose, in children - Growth, cyclosporin, in kidney transplantation.

The use of cyclosporin A (CyA) for immunosuppression after renal transplantation is well established in children [1, 32]. For 50% of all the new transplants performed in children in Europe in 1984, CyA was used as the initial immunosuppressive agent [24]. During the past decade an increasing number of reports have claimed benefits from CyA in pediatric transplantation using different treatment protocols [4, 6, 7, 11, 12, 14, 16, 21, 25, 29]. Compared with conventional therapy using azathioprine (AZA) and corticosteroids, the administration of CyA with or without small doses of steroids appears to be associated with better graft survival rates and fewer rejection episodes. However, it is still debated which regimen facilitates optimal immunosuppression while minimizing side effects. High doses of CyA may reduce the glomerular filtration rate (GFR) and have led to permanent renal dysfunction in adult patients [10, 13]. Therefore, it has been proposed that low doses of CyA be combined with moderate doses of corticosteroids and/or other immunosuppressive agents [3, 27, 31]. We report here on the results of a therapeutic protocol in children in which low-dose CyA is combined with oral methylprednisolone. This regimen is compared with conventional immunosuppressive therapy using AZA and steroids.

Patients and methods

From January 1978 to January 1987, 51 first cadaveric renal transplants were performed in patients aged 2-19 years at the Heidelberg University Hospital. All patients were followed up by the Division of Pediatric Nephrology. The patients were divided into two groups, depending on the treatment they were given. Group AZA consisted of 23 patients transplanted between January 1978 and February 1984 who received AZA and corticosteroids for baseline immunosuppression. Group CyA comprised 28 children grafted between March 1984 and January 1987 who were treated with low-dose CyA and corticosteroids. In both groups surgical techniques, rejection therapy, and immunological conditions were similar. Patients received at least 3 units of packed red cells before grafting The clinical characteristics of these two groups were not significantly different, except that continuous ambulatory peritoneal dialysis (CAPD) prior to transplantation was used more frequently in group CyA than in group AZA (Tables 1 and 2). The last clinical assessment was in March 1989 for the majority of patients. The minimum follow-up period was 4 years for group AZA and 2 years for group CyA.

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Table 1. Clinical and immunological characteristics of 51 transplanted pediatric patients. *$P < 0.01$ (Fischer's exact test)

		Group AZA	Group CyA
Males/females		14/9	15/13
Age in years:	median	12.9	12.9
	range	2.6-17.8	3.1-19.6
Previous dialysis treatment			
Time in months:	median	17	21
	range	6-53	7-58
Type:	hemodialysis	23	18
	CAPD	2	12
Cold ischemia time in hours:	median	23.5	22.0
	range	17-34	11-30
Number of mismatches per patient			
HLA-A,B:	Mean	2.4	2.2
	±SD	±1.3	±1.1
HLA-DR:	Mean	0.8	0.9
	±SD	±0.8	±0.6
Number of kidney donors ≤3 years of age		2	3

Table 2. Distribution of primary renal disorders

	Group AZA	Group CyA
Obstructive uropathy	5	6
Focal and segmental glomerulosclerosis	5	6
Other forms of glomerulonephritis	3	5
Hypoplasia/dysplasia	4	2
Nephronophthisis	1	1
Cystinosis	0	4
Other	5	4
Total	23	28

For immunosuppression all patients in group AZA received AZA in an initial dose of 150 mg/m^2 intraoperatively. Thereafter, AZA was reduced according to the leukocyte count. CyA was started intraoperatively and continued with 150 mg/m^2 per day IV during the first 2-5 days. Therapy was then switched to the oral preparation with doses ranging between 120 and 400 mg/m^2 per day given twice daily in order to achieve target trough levels of 400 ng/ml in the 1st week, 300 ng/ml in the following 3 weeks, and 200-250 ng/ml thereafter. CyA trough whole blood levels were measured daily by RIA within the first 4 weeks and at least once weekly thereafter. In May 1987, RIA testing was modified, resulting in 30% lower values than those obtained according to the previous standards. Both RIA tests were based on the same polyclonal antibody. In this report, results from the second RIA assay are excluded.

Corticosteroids were given to all patients. The amount of IV methylprednisolone given on the day of transplantation varied between 40 and 100 mg/m^2. Thereafter patients were given oral methylprednisolone (and, in a few cases, prednisone). The daily dose was gradually reduced to a minimum of 4 mg methylprednisolone per m^2 per day. Some patients received steroids on alternate days after having obtained a stable clinical condition 1 year or more after transplantation.

A reversible rejection episode was defined as a rise in serum creatinine by 0.3 mg/dl or more that responded to IV methylprednisolone pulse therapy given on 4 successive days (400, 200, 200, and 100 mg/m^2 per day). If there was no response to the pulse treatment, a transplant biopsy was performed. This occurred in most of the patients in group CyA. In the event of an acute vascular rejection identified histologically, a 3-week cycle of antilymphocyte globulin (ATG, Fresenius, Bad Homburg, FRG) was started, something which was, on occasion, combined with plasma exchange.

After the immediate postoperative period, renal function was followed by measuring serum creatinine every 1-3 weeks in group AZA and once weekly in group CyA and by creatinine clearance using 24-h urine samples less frequently.

Actuarial patient and graft survival rates were calculated by life table analysis (Kaplan-Mayer method) and *P* values by the Wilcoxon test. Growth was analyzed by the standard deviation score for height using the data of the Zurich longitudinal growth study [22].

Results

Immunosuppression

The median dose AZA in group AZA varied minimally over time. It was 69 mg/m^2 per day at 3 months and at 1 year and 59 mg/m^2 per day at 4 years. The median CyA dose was 143 mg/m^2 per day at 1 month, 122 mg/m^2 per day at 3 months, 109 mg/m^2 per day at 1 year, and 118 mg/m^2 per day at 4 years after transplantation. The median CyA trough levels were 251 ng/ml after 1 month, 201 ng/ml after 3 months, 206 ng/ml after 1 year, 219 ng/ml after 2 years, and 241 ng/ml after 3 years.

Between 1 and 18 months after transplantation, the oral doses of methylprednisolone were significantly lower in group CyA than in group AZA. The corresponding median methylprednisolone doses were 23.9 and 10.6 mg/m^2 per day at 1 month, 12.1 and 7.1 mg/m^2 per day at 3 months, 6.3 and 4.2 mg/m^2 per day at 1 year, and 3.9 and 5.6 mg/m^2 per day at 4 years for group AZA and group CyA, respectively.

In two group AZA patients, the immunosuppression was supplemented with CyA because of chronic rejection. This resulted in no clinical benefit of renal function (Table 3). Five of the 28 patients in group CyA were switched from CyA to AZA or received additional AZA (i.e., triple therapy) 1-18 months after transplantation. The reason for discontinuing CyA was presumed to be nephrotoxicity. Switching from low-dose CyA to AZA did not lead to improved renal function; two of the three grafts in which CyA was discontinued were lost as a result of irreversible rejection 2-3 months after switching.

Patient and graft survival

No patient died following a first transplant. Actuarial graft survival is presented in Fig. 1. For the sake of comparison, a historical group (AZA_{HIST}) of 28 pediatric patients, each of whom had received a first cadaveric transplant between August 1969 and December 1977, was added [17, 26]. The cadaver donor 1-year graft survival rate was 53% in group AZA_{HIST}, 72% in group AZA, and 78% in group CyA. At 2 and 4 years, the graft survival rate was 68% in group AZA; it remained 78% in group CyA. Groups AZA and CyA differed significantly up to 4 years post-transplantation ($P<0.01$) compared to group AZA_{HIST}, but there was no significant difference between group AZA and group CyA. Graft loss was due to rejection in group CyA with two exceptions: one graft was lost due to primary nonfunction (a 2-year-old multiorgan donor) and one to thrombosis of the graft renal artery (donor age 2 years).

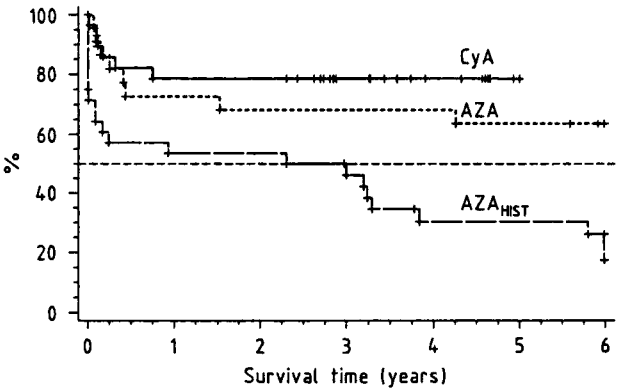

Fig. 1. Actuarial graft survival of groups AZA ($n=23$) and CyA ($n=28$) compared with a historical group of pediatric patients from 1969 to 1977 treated with conventional immunosuppression. Every *vertical dash* indicates a censored observation. Group AZA_{HIST} ($n=28$) is statistically different from the two other groups

Renal function and rejection episodes

Serum creatinine levels of groups AZA and CyA did not differ significantly although values were higher in group AZA 3 years after grafting (Table 4). The median creatinine clearance was 79, 69, and 51 ml/min/1.73 m^2 for group AZA and 78, 63, and 68 ml/min/1.73 m^2 for group CyA 1, 2, and 3 years after grafting, respectively. Differences between groups were not significant.

Within the 1st year posttransplantation, 71% of the patients in group AZA and 78% in group CyA had at least one rejection episode. The actuarial cumulative number of reversible rejection episodes per patient was also similar: 1.4 for group AZA and 1.6 for group CyA in the 1st year and 1.7 for group AZA and 1.9 for group CyA in the first 2 years post-transplantation, respectively.

Complications

CyA nephrotoxicity as suggested by an unexplained increase in serum creatinine was not demonstrated histologically in seven cases. A slight increase in body hair on the neck or back was noted in a few patients in group CyA, but obvious hypertrichosis was never observed. A slight degree of gingival hyperplasia was present in half of the patients receiving CyA. Cushingoid features were common findings in

Table 3. Switching of immunosuppressive therapy in seven transplanted children

Patient (initials)	Month/year grafted	Month/year therapy was switched	Therapy switched from/to	Serum creatinine		Reason for switching
				When switched	As of 3/89	
Group AZA						
G.J.	2/83	11/87	AZA/triple	2.9	8.5	Chronic rejection
N.A.	4/83	6/85	AZA/triple	1.5	2.5	Chronic rejection
Group CyA						
S.D.	4/84	10/85	CyA/triple	1.5		Chronic rejection
		4/86	triple/AZA	1.5	3.1	CyA toxicity?
K.N.	8/84	7/85	CyA/AZA	1.6	2.9	CyA toxicity?
K.M.	12/84	6/85	CyA/AZA	2.2	9/85 rejection	CyA toxicity?
H.G.	5/85	6/85	CyA/AZA	1.3	8/85 rejection	CyA toxicity?
M.I.	12/85	1/86	CyA/triple	1.7	3.2	Low blood levels Poor absorption?

Table 4. Median serum creatinine

Months after grafting	Serum creatinine (mg/dl)	
	Group AZA	Group CyA
12	1.0 ($n=15$)	1.1 ($n=23$)
24	1.3 ($n=15$)	1.1 ($n=19$)
36	1.5 ($n=12$)	1.1 ($n=10$)
48	1.4 ($n=11$)	2.0 ($n=4$)

groups AZA_{HIST} and AZA treated with relatively high doses of corticosteroids [17]. The introduction of low-dose steroid therapy reduced the incidence and severity of cushingoid features.

Arterial hypertension was present and/or antihypertensive treatment was given in half of the patients in group AZA and in 80% of those in group CyA at 1 year post-transplantation. Renal artery stenosis was found in one boy in group AZA (donor age 2 years) and in two children in group CyA (donor age 3 years and adult donor kidney with 3 arteries). One boy in group CyA with the initial lesion of focal and segmental glomerulosclerosis required bilateral nephrectomy of his native kidneys following failure of intensive antihypertensive treatment (including captopril).

Seizures were observed only once in an epileptic boy after accidental withdrawal of valproate therapy; tremor was never observed. In group CyA a transient increase in serum transaminases was seen in one child who was HbSAg-positive. Another child in group CyA showed exacerbation of chronic pancreatitis. Recurrent nephrotic syndrome in the presence of primary focal and segmental glomerulosclerosis was noted in two of five patients in group AZA and in two of six patients in group CyA. One patient in group CyA with proteinuria up to 4 g/m^2 per day developed de novo membraneous glomerulonephritis 9 months after transplantation (primary renal disease: Alport syndrome).

None of the patients in group AZA or CyA suffered from life-threatening ilnfections or a febrile urinary tract infection. Conversion of cytomegalovirus (CMV) or Epstein-Barr virus titers was observed several times, but only one girl in group AZA developed irreversible rejection associated with graft rupture probably related to CMV infection.

Growth

As for linear growth, the median standard deviation score for height was −1.2 at transplantation, −1.4 at 2 years, and −1.1 at 3 years after grafting in group AZA; it was −1.9, −2.1, and −1.6 in group CyA. Only five patients remained prepubertal during the first 3 years after transplantation. The changes in height standard deviation score in these patients did not differ significantly from those in the pubertal transplant recipients.

Discussion

A number of therapeutic regimens with CyA as the primary immunosuppressive agent have been proposed for the management of children following transplantation [32]. In the beginning of the CyA era, the regimens followed the protocols of the large, randomized, multicenter studies performed in adult patients, in which a high, initial oral dose of up to 15-17 mg/kg per day with or without additional corticosteroids was used [10, 13]. With such regimens graft survival in children was found to be superior and rejection episodes less frequent than in children treated with conventional therapy (i.e., AZA plus steroids) [11, 21, 24, 29]. Although untoward effects from steroid therapy could largely be avoided, this was achieved at the cost of a significant reduction in renal function 1-2 years after transplantation as a result of CyA nephrotoxicity [6, 11, 14, 29]. A recent report of the European Dialysis and Transplantation Association indicates that 2-4 years post-transplantation, increased serum creatinine levels are found about twice as often in pediatric patients receiving CyA as in those not receiving this drug [8]. In addition, a number of untoward effects have been noted from high-dose CyA therapy: hypertension [5], hirsutism, gingival hyperplasia, and seizures [12, 13, 29]. Subsequently, attempts to avoid nephrotoxic and other side effects of CyA, either by reducing the dose rapidly or limiting use of the drug to a short period after grafting [16] or by delaying the start of CyA therapy, have been proposed [3]. Other protocols have adopted the use of triple or quadruple therapy by combining CyA with AZA and antilymphocyte globulin [27, 31]. These recent pediatric studies have reported only preliminary results, and no consensus regarding a definitive immunosuppressive regimen in transplanted children can be recommended at present.

Our protocol, which combined relatively low doses of CyA and steroids, followed a similar regimen proposed for adult patients [28, 30]. The graft survival rate and the frequency of rejection episodes with our CyA regimen were comparable to those reported by other authors in transplanted children using higher doses of CyA with or without low doses of steroids [6, 11, 12, 29]. It should be noted, however, that the actual doses of steroids ad-

ministered to these children were not provided in any of these reports [3, 4, 6, 7, 11, 16, 21, 27, 29, 31].

Compared to our group AZA or to other pediatric protocols using AZA [16, 19], graft survival rates after 1-4 years were slightly, but not significantly, higher following the introduction of CyA. This was in contrast to the great difference in graft survival between our two successive groups treated with conventional immunosuppression (Fig. 1). We found about a 20% lower graft survival in the children in group AZA_{HIST} transplanted between 1969 and 1977 than in the later AZA series. This difference may be attributed to a number of factors, such as better preparation for grafting, including refined dialysis techniques, improved nutritional state, improved tissue typing and matching, the deliberate use of blood transfusions, and improved immunosuppressive therapy, including antilymphocyte globulin for rejection therapy [26].

The maintenance of good renal function is critical for the late outcome of transplanted patients [9]. Although renal function in group CyA could be followed for only 3 years in a sufficient number of children after transplantation, we believe that our data suggest an important trend. From 6 months to 3 years after grafting, serum creatinine levels and creatinine clearance were not significantly different in the CyA-treated children than in group AZA. The maintenance of a relatively good initial glomerular function in group CyA should be stressed in view of less favorable results reported in transplanted children treated with higher doses of CyA [11, 12, 14]. As an example, at 1 year after transplantation, Hoyer et al. [11] found a mean GFR (calculated by the formula used by Schwartz et al.) of 46 ml/min/1.73 m^2 in children on CyA therapy compared to 68 ml/min/1.73 m^2 in those given conventional immunosuppression. However, a comparison of the results of CyA therapy obtained in earlier pediatric studies is difficult because of the varying numbers of related donor grafts. In the only single center study in which first cadaver donor transplants were analyzed separately in a comparable group of children, graft survival after 3 years was 75% in the presence of a slightly higher dose of CyA than that used by us [6]. The trend toward a decrease in GFR that we found in CyA-treated children 4 years after grafting might herald a progressive loss of renal function with longer periods of observation, even with the low doses of CyA applied in our series. Recent warnings about the continuous use of CyA [18] may, therefore, be justified.

Retarded growth, as observed in many children on conventional immunosuppressive regimens, was reported to improve under CyA treatment [2, 14, 15, 29], especially in the absence of steroid therapy. Our results do not confirm these observations, something which is in agreement with two other recent reports [3, 7]. The variable results might be explained by unequal status of pubertal maturation, different schedules of steroid administration, or other factors discussed elsewhere [23].

We conclude that transplanted children treated with low-dose CyA (80–150 mg/m^2 per day) plus moderate doses of methylprednisolone (4–7.5 mg/m^2 per day) have similar graft survival, number of rejection episodes, and renal function when assessed up to 3 years post-transplantation and compared to children treated with conventional immunosuppression. Nephrotoxicity as a main side effect of CyA may largely be avoided by this regimen. Further evaluation of immunosuppressive schedules combining CyA, AZA, antilymphocyte globulin, and corticosteroids [27] appears to be important for improving graft survival and for minimizing drug side effects while maintaining satisfactory renal function. CyA should be used with special care in children receiving cadaver kidneys from very young donors because of the high incidence of vascular complications in this age group [16]. Future studies assessing the value of CyA for transplantation should also consider the influence of the more rapid drug clearance in children as compared to adults [12] and the influence of both cold ischemia time and donor and recipient age on graft survival [20].

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