Long-Term Results of Cyclosporin A Therapy in Children

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ABSTRACT

In order to assess the long-term effectiveness and tolerability of cyclosporin A (CsA) treatment in children with renal transplantation (Tx), the follow-ups of 32 children (17 boys, 15 girls; age at Tx = 12.2 yr; range, 5.1 to 16.9) with a functioning graft of ≥5 yr and continuous treatment with CsA and low-dose prednisolone are analyzed retrospectively. For comparison, data of 34 children (19 boys, 15 girls; age at Tx, 11.0; range, 3.2 to 17.1) are collected who had received a graft before the introduction of CsA, had at least 5 yr of graft function, and were continuously treated with azathioprine (AZA) plus high-dose prednisolone. The mean observation period in the CsA group was 6.5 (range, 5.0 to 8.0) yr, and in the AZA group was 10.4 yr (range, 5.7 to 15.8). CsA dosage remained unchanged in the range of 200 mg/m²/day; CsA whole blood trough level was 120 to 130 ng/mL throughout the years. One patient died in each group. Four more grafts were lost in the CsA group by chronic rejection, which was associated with noncompliance in three, and two grafts were lost in the AZA group by chronic rejection. Late acute reversible rejection episodes occurred more frequent in the CsA (six) than in the AZA group (two). The overall survival rates for patients and grafts were significantly better with CsA. The graft function in CsA-treated recipients was significantly lower than that in AZA patients, but there was no progressive loss over the years. Levels of serum uric acid, triglycerides, cholesterol and very low-density lipoproteins were significantly elevated in the CsA group. Hypertension was very frequent in both treatment groups, with a higher percentage of patients treated with antihypertensive drugs under CsA. Adult height was better in males under CsA, but not in females. It is concluded that CsA has proved to be effective and tolerable in long-term immunosuppression; however, its side effects, especially nephrotoxicity, enhance the risk factors for cardiovascular complications in later life.

Key Words: *Cyclosporin A, renal transplantation, azathioprine*

Posttransplantational immunosuppression with cyclosporin A (CsA) was started at our unit in September 1982. Since then, all children with a renal transplant were treated with the same immunosuppressive protocol in which CsA was combined with low-dose prednisolone (1). Results on short-term patient and graft survival, graft function, and side effects have been reported repeatedly (2–6). Because time has passed, it is possible to assess the long-term results in these patients. Therefore, all transplanted children and adolescents who had a functioning graft for more than 5 yr and who received a continuous immunosuppression with CsA are evaluated. Special attention is paid to the graft function, blood pressure, and long-term side effects of CsA. The CsA patients can be compared with those transplanted in an earlier period, who had been treated with azathioprine (AZA) and higher doses of prednisolone (7,8) in our unit since 1973, in order to elucidate special characteristics of CsA treatment.

PATIENTS AND METHODS

In January 1991, a total of 32 patients (17 boys, 15 girls) could be evaluated who had a functioning graft under CsA for 5 yr or more. Their mean age at transplantation, the sources of graft, and the number of transplantations are listed in Table 1. The comparison group of conventional treatment consisted of 34 children (19 boys, 15 girls) who were transplanted in our center between 1973 and 1982 and who were continued on AZA and high-dose steroids (7,8). Except for time of transplantation and immunosuppressive treatment there were no differences between both groups (Tables 1 and 2). Because CsA treatment was started when conventional treatment was stopped, the mean observation period and the number of patients that could be evaluated in the yearly intervals are quite different. The number of patients for the successive intervals up to 8 yr after transplantation is shown in Table 3. The decline of CsA patients is mainly because of the endpoint of the

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TABLE 1. Long-term follow-up after kidney transplantation (5 or more yr)

	CsA ($N = 32$)	AZA ($N = 34$)
Period	9/82–1/86	6/73–9/82
Boy/Girl	17/15	19/15
Transplant Age (yr)		
Mean	12.2	11.0
Range	5.1–16.6	3.2–17.1
Live Renal Donor/Cadaveric Donor	6/26	13/21
1./2./3.Tx	29/1/2	29/4/1

TABLE 2. Long-term follow-up after kidney transplantation

Original diseases	CsA	AZA
Congenital/Familial	22 (69%)	22 (65%)
Dysplasia/hypoplasia	6	4
Nephronophthisis	3	6
Cystinosis	4	7
Familial nephropathy	2	2
Obstructive uropathy	5	3
Multicystic kidneys	2	
Acquired	10 (31%)	12 (35%)
Hemolytic uremic syndrome	2	4
Focal segmental glomerulosclerosis	3	2
Schönlein-Henoch glomerulonephritis		3
Membranoproliferative glomerulonephritis	2	
Chronic glomerulonephritis	3	3

TABLE 3. Long-term follow-up after kidney transplantation 5 or more yr posttransplant

Posttransplant Period (yr)	CsA (N)	AZA (N)
Mean (Range)	6.47 (5.03–8.01)	10.4 (5.70–15.80)
≥5	32	34
≥6	20	33
≥7	13	29
≥8	3	28

observation period, whereas in AZA patients, it is caused by graft failures.

GFR was estimated from plasma creatinine and body length, by the formula of Schwartz *et al.* (9), which was found to be suitable for transplanted children (3). Laboratory tests were performed by standard laboratory procedures at patients' visits to the outpatient clinic. Lipid analysis was performed with lipoprotein electrophoresis, with agarose gel (10). CsA whole blood trough levels were measured by a monoclonal RIA (11). The determinations of height and bone age were done as described elsewhere (12).

For statistical analysis, a two-tailed t test for unpaired samples and a χ^2 test were used.

RESULTS

Survival of patients after they had completed at least 5 yr with a functioning graft was the same in both immunosuppressive protocols. Two patients died within the observation period, one in each group. A CsA-treated boy with cystinosis died suddenly 5.9 yr after transplantation with a well-functioning graft. The possible cause of death was an acute obstructive respiratory infection. A girl under AZA died 7.5 yr after transplantation with a badly functioning graft because of fungal sepsis.

The graft survival in patients who had lived with a functioning graft for at least 5 yr after transplantation is shown on Figure 1. In CsA-treated patients, a total of five grafts were lost, four because of chronic rejection (5.3, 5.7, 5.8, and 7.5 yr after transplantation) and one because of patient death. In three out of four patients with chronic rejection, noncompliance was evident. In the AZA-treated group, three grafts were lost, two because of chronic rejection (at 6.2 and 6.8 yr after transplantation) and one because of death of the patient. The comparison of graft survival in both groups reveals a tendency for less-favorable long-term outcome in CsA-treated patients, although the difference is far from statistical significance because of the low number of cases in the CsA group.

However, these figures describe only the outcome of those patients who had already lived with a functioning graft for more than 5 yr. They do not describe the overall effect of immunosuppression after kidney transplantation in children. For the latter, one has

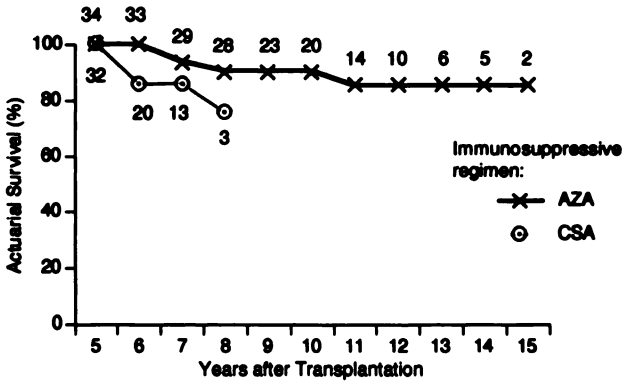

Figure 1. Graft survival in children with a functioning renal transplant for more than 5 yr, treated either with CsA or AZA.

to analyze the overall survival rates, *i.e.*, include the first 5 yr of all children transplanted within the whole period and treated either with AZA or with CsA. This is done in Figure 2.

The immunosuppression beyond the fifth year continued unchanged in the majority of cases with CsA. The mean dose of CsA did not change during the following years (Table 4); it remained in the range of 200 mg/m^2/day (5 to 7 mg/kg/day) given in two divided doses. The mean whole blood trough levels were kept in the range of 120 to 140 ng/mL. The daily prednisolone dose was between 2.5 and 5 mg, applicated as a single morning dose. However, in some patients, AZA had to be added as triple therapy because of suspected CsA nephrotoxicity in two patients, noncompliance with low CsA blood levels in five patients, and deterioration of graft function in three patients. Thus, 5 out of 32 patients had triple therapy in the fifth year, 2 of 20 in the sixth year, 5 of 13 in the seventh year, and 2 of 3 in the eighth year.

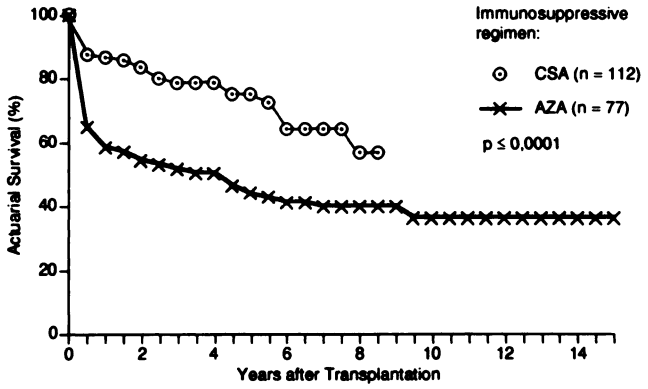

Figure 2. Overall graft survival in all children who received a renal transplant between 1973 and 1990 at our unit, treated either with CsA or AZA.

TABLE 4. Immunosuppressive treatment with CsA (Mean ± SD)

Posttransplant (yr)	Dose (mg/m^2/day)	Whole Blood Trough Level (ng/mL)	Prednisolone (mg/m^2/day)
5	207 ± 49	134 ± 65	2.64 ± 0.94
6	199 ± 41	132 ± 41	2.75 ± 1.05
7	194 ± 61	122 ± 31	2.47 ± 1.51
8	201 ± 43	130 ± 21	1.67 ± 0.24

Late acute rejection episodes occurred in spite of this immunosuppressive regimen even after 5 yr of graft function: in the CsA group, five times in the sixth year and once in the seventh year; in the AZA group, only twice in the eighth year. All acute rejection episodes responded to prednisolone pulse therapy, but one graft was lost subsequently. It was uncertain to what extent medical noncompliance was related to these rejection episodes, which obviously occurred more frequently in the CsA than in the AZA group.

Graft Function

Rehabilitation depends on graft function and dosage of immunosuppressive drugs with side effects. Graft function was studied in both treatment groups 5 to 8 yr after transplantation (Table 5). It is obvious that GFR was significantly lower in CsA-treated patients than in AZA-treated ones. In most patients, *i.e.*, those who did not reject graft, GFR remained stable, because there was only a minimal decline of mean values in either group.

Values of serum creatinine and urea are shown in Table 6. For creatinine, the mean values under CsA were moderately elevated, and under AZA, the values were slightly elevated but lower than CsA values; most differences, however, were statistically not significant. Urea was definitively elevated under CsA, whereas under AZA, the values were near normal. The differences between CsA and AZA were statistically significant for all posttransplant years studied. There were no progressive increase over the years in either group.

Further Laboratory Investigations

Further laboratory tests were done routinely in CsA-treated patients only, in order to rule out the

TABLE 5. GFR in children 5 or more yr posttransplant

Posttransplant (yr)	CsA		AZA		*P*
	(*N*)	(mL/min/1.73 m^2)	(*N*)	(mL/min/1.73 m^2)	
5	32	38.6 ± 17.6	34	63.0 ± 26.5	0.0001
6	20	41.1 ± 7.6	33	58.8 ± 23.4	0.0083
7	13	37.3 ± 9.4	29	62.5 ± 22.6	0.0014
8	3	36.3 ± 18.2	28	59.9 ± 25.2	0.13

TABLE 6. Serum creatinine and urea (mean ± SD) levels in children with graft function of 5 or more yr

Posttransplant (yr)	Creatinine		P	Urea		P
	CsA	AZA		CsA	AZA	
	(μmol/L)			(mmol/L)		
5	193 ± 127	131 ± 144	0.07	13.5 ± 7.4	7.8 ± 7.3	0.0027
6	211 ± 174	150 ± 195	0.25	17.1 ± 14.7	7.6 ± 7.6	0.0035
7	221 ± 138	110 ± 61	0.0008	14.3 ± 9.5	6.4 ± 5.5	0.0017
8	206 ± 113	113 ± 68	0.04	15.0 ± 7.8	6.3 ± 4.4	0.0052

TABLE 7. Laboratory blood findings in CsA-treted children with graft function of 5 or more yr

Posttransplant (yr)	Uric Acid (μmol/L)	Magnesium (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)	Bilirubin (μmol/L)	Aspartate Aminotransferase (U/L)	Hemoglobin (g/dL)
5	486 ± 102	0.78 ± 0.10	4.6 ± 0.5	23.4 ± 3.0	8.6 ± 4.1	10 ± 3	11.4 ± 2.3
6	526 ± 128	0.80 ± 0.09	4.6 ± 0.7	23.8 ± 3.4	7.4 ± 4.3	9 ± 3	11.2 ± 2.8
7	489 ± 100	0.76 ± 0.10	4.4 ± 0.6	20.6 ± 3.4	7.5 ± 2.6	9 ± 3	10.8 ± 2.6
8	548 ± 134	0.83 ± 0.08	4.4 ± 0.3	21.9 ± 0.4	9.0 ± 6.9	10 ± 4	11.0 ± 4.2

toxicity of the drug. Results of blood examinations are shown on Table 7. Uric acid was significantly elevated and remained high throughout the observation period. Only one patient developed symptoms of gout 8 yr after transplantation. Magnesium was low normal, but no child showed clinical signs of magnesium depletion. Potassium remained within the normal range, as did bicarbonate. There were no signs of hepatotoxicity, *i.e.*, bilirubin and aspartate aminotransferase (glutamic-oxaloacetic transaminase) remained completely normal, as did alanine aminotransferase, CHE, and gammaGT (not shown). Hemoglobin levels stayed in the low normal range; hemoglobin A1c was elevated in those cases studied, *i.e.*, mean value was 4.54 ± 0.69%.

Lipoprotein metabolism was studied only recently, when serum concentrations of triglycerides, total cholesterol, pre-β-lipoprotein (very low-density lipoprotein), β-lipoprotein (low-density lipoprotein), and α-lipoprotein (high-density lipoprotein) were determined by lipid electrophoresis. Values derived from 26 children treated with CsA (mean age, 17.6 ± 3.4 yr; mean posttransplant function, 5.8 ± 1.1 yr) and 21 children treated with AZA (mean age, 22.2 ± 3.4 yr; mean posttransplant function, 11.2 ± 2.1 yr) are shown in Table 8. There was a significant increase of triglycerides and VLDL in the CsA group and a lower value for HDL, compared with AZA-treated children, whereas total cholesterol and LDL were not different; however these latter values were increased as compared with normal levels.

TABLE 8. Serum lipid levels in children with graft function of 5 or more yr (mean ± SD)

	CsA (N = 26)	AZA (N = 21)	P
	(mg/dL)		
Triglycerides	189 ± 80	124 ± 45	0.002
Cholesterol	218 ± 51	198 ± 50	0.193
VLDL (pre-β)	35 ± 25	20 ± 9	0.016
LDL (β)	136 ± 49	124 ± 42	0.410
HDL (α)	47 ± 14	54 ± 12	0.081

Hypertension

The mean values of blood pressure registered at routine visits to the outpatient departments are shown in Table 9. Both the systolic and diastolic pressures were above the normal mean for age. There was a tendency for higher values in CsA-treated patients; the difference, however, was not significant. Antihypertensive treatment was needed in the great majority of patients, with higher percentages in the CsA than the AZA group, and most of them received two to four antihypertensive drugs. Sequelae of long-standing hypertension, *i.e.*, left ventricular hypertrophy and hypertensive retinal arteriolopathy, were seen in half of the cases.

TABLE 9. Blood pressure in children with graft function of 5 or more yr

Posttransplant (yr)	Systolic (mean ± SD; mm Hg)	Diastolic (mean ± SD; mm Hg)	Antihypertensive Treatment[a] (% of patients)	Mean Number of Antihypertensive Drugs
CsA				
5	131 ± 15	87 ± 11	84.4	2.63 ± 1.24
6	133 ± 14	85 ± 17	95.0	2.70 ± 1.03
7	133 ± 15	84 ± 13	92.3	3.08 ± 1.32
AZA				
5	127 ± 11	83 ± 10	76.5	2.51 ± 1.10
6	126 ± 14	83 ± 12	75.7	2.40 ± 1.00
7	130 ± 12	85 ± 10	72.4	2.50 ± 1.20

[a] Furosemide not included.

Adult Height

The adult height was considered to be achieved when the epiphyseal plates were closed and bone age had reached 16 yr in girls or 18 yr in boys (12). This was the case in 13 patients (5 boys, 8 girls) under CsA and 16 patients (10 boys, 6 girls) under AZA immunosuppression. The final heights are shown in Table 10. Boys had achieved a satisfactory mean height under CsA, but not under AZA, whereas girls had similar heights in both groups. As can be recognized from the mean ages at the time of transplantation, the groups are not as homogeneous as one would have liked for comparison.

TABLE 10. Adult height achieved in patients with graft function of 5 or more yr (mean ± SD)

	CsA	AZA
Boys		
N	5	10
Age at Transplant (yr)	15.4 ± 1.4	13.6 ± 1.7
Adult Height (cm)	174.1 ± 4.4	166.5 ± 9.6
Girls		
N	8	6
Age at Transplant (yr)	14.7 ± 1.7	13.6 ± 1.8
Adult Height (cm)	157.7 ± 8.8	158.9 ± 4.7

Side Effects

Extrarenal side effects of long-term CsA treatment not mentioned above are listed in Table 11. The overall incidence was low, gingival hyperplasia being the most prominent side effect. Other signs were rare and less severe than during the early months of CsA treatment when the CsA dose administered was much higher. In our renal patients, there were no malignancies, no cerebral disturbances such as seizures or tremor, and no immunological deficiencies during the 5 to 8 yr under CsA treatment.

The severity of gingival hyperplasia was investigated with special focus on the simultaneous administration of nifedipine (13). Hyperplasia was graded according to severity in stage I (mild) to stage III (severe, indicative of gingivectomy). As controls, transplanted children under AZA were studied. The results are shown in Table 12. AZA treatment alone or in combination with nifedipine did not lead to gingival hyperplasia. CsA treatment alone was associated with slight to moderate gingival hyperplasias, which was much more severe when nifedipine was added. It is, therefore, our policy today to avoid nifedipine if CsA treatment is indicated.

TABLE 11. Extrarenal side effects of CsA in children 5 or more yr after transplantation[a]

Gingival hyperplasia	16/24 (67%)
Adenoids	3/32 (9%)
Hypertrichosis	2/32 (6%)
Severe infection	1/32 (3%)
Fibroadenoma	1/32 (3%)

[a] No malignancy, seizure, tremor, or immunodepletion.

TABLE 12. Gingival hyperplasia in transplanted children

Immunosuppression	*N*	Without Nifedipine at Stage:				With Nifedipine at Stage:			
		0	I	II	III	0	I	II	III
AZA	19	14				5			
AZA/CsA	41	9	5		1	4	9	7	6
CsA	46	8	10	2		2	7	3	14

DISCUSSION

The posttransplantational immunosuppression with CsA was introduced in adults more than 10 yr ago (14) and soon proved to be superior to conventional immunosuppression with AZA, with regard to the short-term survival of patients and grafts (15,16). Similar results could be obtained in pediatric patients when adequate effective dosages were achieved (1–4,17,18). In addition to improved survival rates, CsA allowed a definitive reduction of steroid dosage, which resulted in the amelioration of steroid side effects and improvement of growth rates (2,12,19,20).

The major disadvantage of CsA is its nephrotoxicity. It soon became evident that graft function was suppressed by the administration of CsA as compared with conventional immunosuppression, observed in adults (21–23) as well as in children (2,3). CsA was also nephrotoxic in patients with other organ or bone marrow transplantations (24–26) and in the treatment of autoimmune diseases (27,28). Thus, the question was raised and remains unanswered so far as to whether the benefits of CsA outweigh the hazards so that one could continue immunosuppression with CsA indefinitely or whether one has to switch to other immunosuppressive regimens in order to avoid further damage to the patient (29,30).

Our results should be considered as a contribution for the evaluation of long-term CsA effectiveness and tolerance in children. Shortcomings of our analysis are that patients were derived from a single center and, therefore, were small in number, that the observation periods were variable between 5 and 8 yr posttransplantation, that the comparison with the conventional treatment was historical, and that the assessments were made retrospectively. In spite of these limitations, it should be emphasized that the immunosuppressive regimen was not changed throughout the years and that, therefore, all children received the same immunosuppression with, in terms of today's knowledge, relatively high doses of CsA (Table 4). Therefore, it should be possible to evaluate the effects and side effects of CsA in long-term transplantation treatment.

The immunosuppressive effect of CsA remained stable, as evidenced by the few graft losses beyond 5 yr after transplantation. In our group of 32 transplanted patients, five grafts were lost during the following years—three of them associated with noncompliance of the patients and one by the patient's death. Thus, only one patient suffered from chronic rejection despite adequate intake of CsA. In the AZA group, the follow-up after 5 yr of graft function was similar: two grafts were lost by chronic rejection and one by the death of the patient. Comparable results have been reported for adult patients (31–33), which means that the immunosuppressive protection of the graft by CsA remained effective beyond 5 yr after transplantation. Thus, CsA is not only superior to AZA in the first years after transplantation but keeps its effectiveness later on, as demonstrated by the overall survival rates (Figure 2). This is supported by the report that a switch from CsA to AZA 1 yr after transplantation was followed by a poorer outcome in graft survival (29).

Medical noncompliance of the patients is a real threat for long-term immunosuppression. In our CsA-treated group, noncompliance accounted for 10% of graft losses during the observation period. This is in agreement with other reports, in which noncompliance was observed—predominantly in adolescents—in up to 50% of all cases (34,35). One therefore has to realize that psychosocial counseling and guidance are important steps to secure continuous immunosuppression.

Furthermore, the number of acute reversible rejection episodes was higher in the CsA group after 5 yr than in the AZA group. This could indicate that the protocol provides a low level of immunosuppression, which could be jeopardized by noncompliance of patients. Similar observations have been made in adults (36). It could also suggest that noncompliance might be more common in CsA than in AZA treatment. A possible explanation for this could be the kind of application: how CsA had to be taken, *i.e.*, as a liquid diluted in chocolate drink or fruit juice, which were not always available in the adolescents' circumstances. The introduction of CsA capsules will hopefully improve the compliance.

The most important adverse side effect of CsA is nephrotoxicity, which includes impairment of graft function and hypertension. Graft GFR is significantly lower under CsA than under AZA. This has been observed early after transplantation in children (2,3) and adults (16,22,31) and has persisted throughout all observation periods reported (6,22,32,37). In our study, 5 to 8 yr after transplantation, there was a significant difference in GFR between CsA- and AZA-treated patients (Table 5). Renal impairment was associated with elevated levels of serum creatinine and, especially, urea (Table 6). Furthermore, serum uric acid remained elevated and serum magnesium tended to be lower, *i.e.*, findings similar to those observed in our own patients of early posttransplant periods (40,41) and in those from other investigations (42,43).

It is well established that the nephrotoxic effect of CsA depends on the dose and blood level (25). However, within the therapeutic window of CsA, functional impairment of the graft is found in almost all cases regardless of whether CsA dose is large or low and whether CsA is combined with AZA or prednisone or is given as a monotherapy. Obviously, the most important factors for functional impairment are the initial dose and the time of the first CsA

application. In a study of Canafax *et al.* (44), it was shown that a high initial dose (17.5 mg/kg/day) and early start of CsA treatment (within the first week) were associated with significantly higher plasma creatinine levels found subsequently, although CsA doses later on were reduced to 5 to 6 mg/kg/day in all study groups. This corresponds well with reports in which CsA was not started before the graft had resumed its function. Comparison of these treatment groups with conventional AZA treatment groups revealed that there were no or only slight differences in GFR and blood creatinine values thereafter (35,45,46). The main task for the future, therefore, is to secure a potent initial immunosuppression in the early phase posttransplant, if possible without using CsA, which might damage the graft in its most vulnerable phase. Later on, the maintenance immunosuppression can be performed with CsA (as long as other less-toxic drugs are not available) in a low-dose range (5 mg/kg/day or 150 to 200 mg/m^2/day), without jeopardizing the renal function by rejection or nephrotoxicity.

Hypertension is another risk factor that will influence the long-term prognosis of transplanted patients. It has been shown in an earlier study that hypertension was a very frequent finding in both the CsA-treated and AZA-treated groups, ranging from 64 to 83% of cases during the first 5 yr after transplantation (47). Acquired original diseases and cadaveric grafts were associated with higher rates of hypertension than were congenital original diseases and living related donor grafts, respectively. The frequency of hypertension persisted and even increased beyond the fifth posttransplantational year (Table 9). The great majority of cases had to be treated with two to four antihypertensive drugs. In spite of this, the mean values of ambulatory blood pressures were not completely normalized. The longer the posttransplantational period, the more patients required antihypertensive treatment—in the CsA group, almost 100% after 7 yr; in the AZA group, slightly less. Hypertension is a well-known complication of transplantation with CsA treatment (25,48,49). It is obvious that CsA contributes to hypertension by impairing renal function and possibly by leading to arteriolopathy (50). However, CsA alone cannot be incriminated for hypertension, because AZA is also associated with high rates (47,51). Therefore, several factors are involved, such as chronic or acute rejection, renal artery stenosis, urological problems, original diseased kidneys, and recurrence of primary renal disease. It is important to recognize these factors and to treat them if possible, because, in the long run, cardiovascular complications account for the highest rate of adult recipient's mortality.

Changes in lipoprotein metabolism constitute a further cardiovascular risk factor that is associated with impaired renal function, hypertension, and immunosuppressive therapy. In patients treated with CsA plus low-dose prednisone, serum concentrations of triglycerides and VLDL were significantly above those in AZA-plus-prednisone-treated patients (Table 8). In both groups, levels of total serum cholesterol were significantly increased compared with normal levels. Similar data have been described in other groups of transplanted patients, either on conventional immunosuppression (52) or on CsA (53–55). Sequential analysis demonstrated that hypercholesterolemia and hypertriglyceridemia persisted in CsA-treated patients (53), as were also shown in our patients with a mean of 5.8 yr after transplantation. Thus, the combination of increased levels of VLDL, cholesterol, and hypertriglycerides together with a high incidence of hypertension may contribute considerably to morbidity and mortality from arteriosclerotic cardiovascular disease in later life.

Other side effects of CsA were not severe in the long-term observation period (Table 11). The most frequent sign was gingival hyperplasia, which was especially severe when simultaneously nifedipine had been given. All cases with grade III hyperplasia (Table 12) needed surgical gingivectomy. Other side effects were rare and tolerable. We did not observe a malignancy in CsA-treated renal patients; however, two patients under conventional immunosuppression developed cancer (thyroid cancer, seminoma) after 14 and 15 yr posttransplantation, respectively. We did not observe any central or peripheral neurotoxicity. One boy with impaired graft function developed severe pneumonia and needed intensive therapy but recovered. Otherwise, no severe infections were encountered. Thus, long-term CsA was well tolerated, and therefore, no patient needed to be taken off CsA or to be switched to another immunosuppressant.

In conclusion, CsA proved to be effective in the long-term immunosuppression after renal transplantation in children. A comparison of CsA with AZA revealed that the overall survival rates remain superior under CsA treatment. Noncompliance of the patients is the most important risk factor in long-term immunosuppression. Side effects of CsA, namely, impairment of graft function, hypertension, and altered lipoprotein metabolism, remain present after 5 yr of posttransplant treatment but do not or only minimally progress. These changes, however, are high risk factors for cardiovascular complications in later life and, therefore, need to be investigated further and treated consequently. At present, treatment with CsA in lower doses should be continued as maintenance immunosuppression until a less-toxic immunosuppressant becomes available.

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