ABSTRACT
This study presents the 10-yr follow-up results of a multicenter controlled trial on 108 recipients of cadaveric renal transplantation, randomized to receive cyclosporine (N = 55) or azathioprine (N = 53), both in combination with steroids. The 10-yr patient survival rate was 89% in the cyclosporine group and 83% in the azathioprine group (P = not significant (NS)); the 10-yr graft survival was 56% and 35%, respectively (log-rank test, P = 0.009). The half-life of grafts functioning after 1 yr was 15.4 ± 3.9 versus 10.6 ± 3.6, P = NS. The rate of early rejection in the cyclosporine group was significantly lower than that in the azathioprine group (0.30 versus 1.4, P < 0.01). Although the mean creatinine clearance rate was always higher in the azathioprine group, the decline in graft function from the first to the tenth yr was not significantly different between the two groups (-13.0 ± 16.4 versus -12.3 ± 19 mL/min, P = NS). In cadaveric renal transplantation, cyclosporine allows better graft survival than azathioprine, not only in the short term but also in the long term, with similar attrition of graft function for up to 10 yr.

Key Words: Long term, graft half-life, prospective study

Several studies (1–6) have reported better short-term cadaveric graft survival for patients treated with cyclosporine than for those given azathioprine. However, it is still unclear whether this advantage is dissipated in the long term, because cyclosporine may cause vascular and interstitial changes in the kidney (7–9) that could lead to progressive renal failure and graft loss. The results of retrospective analyses of collaborative registries are controversial. In his review of the results of the Collaborative Transplant Study, Opelz (10) reported better 5-yr cadaveric graft survival for patients given cyclosporine than for those given azathioprine. Moreover, a recent retrospective analysis of 1663 renal transplant patients showed no evidence of progressive toxic nephropathy up to 5 yr (11). On the other hand, the data of the University of California at Los Angeles Transplant Registry showed that the half-life of cadaveric kidney transplants was virtually the same before and after the introduction of cyclosporine (12). Unfortunately, these retrospective studies are affected by a number of variables, such as the center effect, the different selection criteria, the accuracy in reporting data and the different periods in which the therapy was given.

Between February and November 1983, we enrolled 108 cadaveric renal transplant patients in a controlled study in which patients were randomized to either cyclosporine or azathioprine at the time of transplantation. The early results of this study have already been published (13). We now report the results after 10 yr.

METHODS

Patients
Cadaveric renal transplantation candidates were eligible for this study unless they were older than 60 yr of age or had severe liver disease, infections, insulin-dependent diabetes, neoplasia, a peptic ulcer, or a fibrotic bladder. Patients who had already rejected two transplants were also excluded. All patients received at least three blood transfusions before transplantation. The randomization, stratified by center, was done immediately before transplantation by opening consecutively numbered treatment-coded envelopes.

Treatment
The patients allocated to azathioprine were treated with the best local immunosuppressive protocol. The initial azathioprine dose was 3 mg/kg per day, adjusted to maintain a peripheral leukocyte count above 5000/μL. All patients received decreasing doses of methylprednisolone iv for 5 days, followed by oral prednisone at different initial doses in the three centers (0.5 to 1 mg/kg per day). Prednisone was gradually tapered to a maintenance dose of 10 mg/day at 12 months after transplantation.

In the cyclosporine group, the patients received an iv infusion of cyclosporine, 5 mg/kg for 2 to 4 days. Subsequently, a single morning oral dose of 15 mg/kg per day was
given, and reduced by 2 mg/kg every fortnight. The maintenance dose was then adjusted to keep the cyclosporine blood levels, as assessed by a polyclonal RIA kit, between 200 and 800 ng/mL in the first month, and then between 200 and 600 ng/mL. After the monoclonal assay became available, blood levels were kept between 100 and 200 ng/mL. Decreasing iv methylprednisolone doses were given for the first 4 days (500, 160, 120, and 80 mg/day), followed by oral prednisone 20 mg per day, tapered to 10 mg per day by the end of the sixth month.

**Graft Rejection**

Acute rejection was defined as an increase in serum creatinine concentration of at least 30% over baseline values that was not justified by any other identifiable cause. In many cases, the diagnosis was supported by a renal biopsy. Rejection was treated with one to five iv methylprednisolone pulses of 0.5 g each, given every 24 to 48 h.

**Treatment Switches**

Cyclosporine toxicity was suspected whenever a slow increase of serum creatinine concentration, associated with normal-high blood levels of cyclosporine, occurred. Diagnosis was indirectly confirmed by a fine-needle biopsy showing isometric vacuolization of tubular cells and/or vascular endothelial cells without signs of inflammation (14) or by a renal biopsy showing tubular or arteriolar toxicity (15) without signs of rejection. After cyclosporine toxicity was confirmed, the dose was decreased by 20 to 30%. It was further reduced to 50% if no improvement was observed; any further lack of improvement led to a switch to azathioprine (3 mg/kg per day) while gradually tapering the cyclosporine dose to 0. The glucocorticoid dose was kept unchanged. In five cases, azathioprine was added to low-dose cyclosporine. In the azathioprine group, in the case of a deterioration in renal function attributable to chronic rejection, cyclosporine rescue treatment was allowed.

**Statistical Analysis**

All statistical evaluations were performed according to the Intention-to-Treat principle. Patient- and graft-survival probability curves, as well as the risk of developing severe/chronic complications, were computed using the Kaplan-Meier product-limit estimate; treatment differences were evaluated using the log-rank test. The transplant half-life (time to the loss of 50% of the grafts functioning after 1 yr) in the two groups was compared using the method proposed by Takiff et al. (16). A backward logistic regression analysis (17) was performed to assess the influence on long-term graft survival of different variables at transplantation (the randomized treatment and the number of A, B, or DR HLA mismatches), and after 12 months (serum creatinine concentration, hypertension, and number of acute rejections). Between-treatment differences of other variables were tested using the Mann-Whitney U test or t test, with the Bonferroni correction for multiple comparisons used where appropriate. Proportions were compared using Fisher’s exact test or the chi-squared test.

**RESULTS**

**Patients**

Fifty-five patients were assigned to cyclosporine and 53 to azathioprine. The median age was comparable in the two groups (33 and 38 yr), although five of the six children aged less than 14 yr were randomized to cyclosporine. In the cyclosporine group, the female-to-male patient ratio was higher (31:24 versus 18:35), and the mean body weight was significantly lower (54.8 ± 16.2 versus 61.9 ± 12.5 kg, \( P = 0.01 \)). All other parameters (HLA mismatches, previous transfusions, second transplants, patients with hypertension, distribution of the original disease, cold ischemia time) were well matched in the two groups.

**Patient Survival**

In the cyclosporine group, the 10-yr patient survival rate before graft loss was 89%, in comparison with 83% in the azathioprine group (Figure 1). Five patients died in the cyclosporine group with functioning transplant: one from a cerebral hemorrhage immediately after transplantation surgery, one from a cerebral lymphoma, two from sepsis, and one from interstitial pneumonia (two of the three deaths for infection occurred after the patient had been switched to azathioprine). There were four deaths in the azathioprine group: one from cardiac infarction, two from systemic infections and one from acute pancreatitis; one patient was lost to follow-up approximately 1 yr after transplant. While in the trial, the death rate per 100 patient-yr was 1.3 in the cyclosporine group and 1.7 in the azathioprine group.

If the deaths after return to dialysis (six in the cyclosporine group and five in the azathioprine group) are also considered, the overall 10-yr patient survival rate was 80% in the cyclosporine group and 82.2% in the azathioprine group (\( P = \text{NS} \)).

**Graft Survival**

The probability of being alive with a functioning graft at 10 yr was 56% in the cyclosporine group and 35% in the azathioprine group (log-rank test, \( P = \text{n.s.} \)).

![Figure 1. Patient and graft survival in patients randomized to cyclosporine (△ on solid line, \( N = 55 \)) and to azathioprine (● on dashed line, \( N = 53 \)). Graft survival is significantly higher in the cyclosporine group (56%) than in the azathioprine group (35%). The numbers over the curves indicate the patients at risk at each time point.](image-url)
The four children aged less than 10 yr were randomized to cyclosporine, and all lost their grafts: three for rejection after respectively 10, 11, and 22 months, and the fourth for the recurrence of glomerulonephritis 22 months after transplantation.

Multivariate analysis showed that higher serum creatinine concentration levels at 1 yr (P < 0.001) and younger age (P < 0.02) significantly correlated with graft failure after the first yr.

Ten of the 19 graft failures in the cyclosporine group were caused by late rejection (18.2%), four by early rejection (7.3%), three by the recurrence of glomerulonephritis (5.5%), and two by surgical complications (3.6%). In the azathioprine group, 19 grafts were lost for early rejection (35.8%), seven for late rejection (13.2%), one for glomerulonephritis recurrence (1.8%), and three for surgical complications (5.7%).

Cyclosporine Dose

The mean cyclosporine dose was 5.4 ± 1.5 mg/kg per day at 1 yr after transplant, 3.7 ± 1.5 after 4 yr, and 3.2 ± 1.2 after 10 yr.

Dose of Steroids

The mean daily dose of prednisone after 1, 5, and 10 yr was, respectively, 8.4 ± 1.6, 6.4 ± 2.0, and 6.0 ± 1.9 mg/day in the cyclosporine group and 10.3 ± 2.5, 8.9 ± 2.1, and 7.4 ± 2.0 mg/day in the control group.

Delayed Renal Function

The percentage of patients requiring dialysis after transplantation because of delayed renal function was similar in the two groups (25% in the cyclosporine versus 28% in controls). The mean duration of dialysis was, respectively, 21.6 ± 19.9 and 17.5 ± 10.3 days (P = NS).

Acute Rejection

All randomized patients, except for one in the cyclosporine group who died immediately after transplantation surgery, were evaluable for rejection. In the cyclosporine group, 22 patients (40.7%) never experienced rejection, in comparison with 9 out of 53 patients (17%) in the azathioprine group (P < 0.006). The mean number of rejections per patient was 0.81 (44 rejections) in the cyclosporine group, and 2.09 (111 rejections) in the azathioprine group (P < 0.01). The mean number of early graft rejections (0 to 3 months after transplantation) per patient was 0.30 (16 rejections) in the cyclosporine arm and 1.4 (74 rejections) in the azathioprine arm (P < 0.01). After the third month, 21 out of 48 patients at risk in the cyclosporine group had 28 rejections (0.58 rejection per patient); in the azathioprine group, 16 out of the 38 patients at risk had 37 rejections (0.97 rejection per patient, P < 0.01). The cumulative number of iv methylprednisolone pulses for acute rejection was lower in the cyclosporine group (74 versus 277, P < 0.001).

Renal Function

If only patients still on the originally randomized treatment after 10 yr are considered, the creatinine clearance rate was always higher in the azathioprine group than in the cyclosporine group at all time points (Figure 2; P < 0.05); however, the decline in creatinine clearance rate over the years was similar in the two groups (−12.3 ± 19 mL/min or −15% versus −13.0 ± 16.4 mL/min or −22%, P = NS).

Change of Therapy

Fourteen of the 55 patients randomized to cyclosporine (25%) were converted to azathioprine because of slow and progressive graft function deterioration that did not improve after cyclosporine dose reduction. Of these patients, two died because of infections (one as a consequence of aplasia because of accidental azathioprine overdosage, and the other had a fatal infection after switching back to cyclosporine because of further progressive renal function impairment) and three had an irreversible rejection (two after reintroduction of cyclosporine). One further patient was successfully reconverted to cyclosporine because of renal impairment progression that was unresponsive to steroid pulses. One patient lost the graft because of chronic rejection about 9 yr after switching from cyclosporine to azathioprine, but the remaining seven still have functioning grafts 10 yr after transplantation, with a mean serum creatinine concentration of

![Figure 2. Creatinine clearance rate from the first to the tenth year after transplantation in patients with functioning grafts still on the originally randomized treatment at the end of the tenth year. (Cyclosporine, a on solid line, N = 23; azathioprine, a on dashed line, N = 16.) The creatinine clearance rate was higher in the azathioprine group (between-group comparison P < 0.05, t test with Bonferroni correction for multiple comparisons). The decreases in the creatinine clearance rate in the cyclosporine group (−13.0 ± 16.4 mL/min) and in the azathioprine group (−12.3 ± 19.0 mL/min) were not significantly different.](image)
1.2 ± 0.30 mg/dL (109 ± 27 μmol/L). On the whole, the conversion to azathioprine was successful in eight of 14 patients (57%).

After 10 yr of follow-up, of the 31 cyclosporine-randomized patients with functioning grafts, 24 (77%) were still being treated with cyclosporine (alone or in combination with steroids, azathioprine, or both); the remaining seven (23%) were those who had been switched to azathioprine and steroids. On the other hand, of the 18 azathioprine-randomized patients with a functioning graft after 10 yr, 15 (79%) were still on azathioprine-steroid therapy, two (11%) have been switched to cyclosporine because of late progressive rejection, and one (6%) has been switched to cyclophosphamide because of liver toxicity.

**Severe Infections and Neoplasia**

In the cyclosporine group, 11 infections requiring hospitalization were observed: four for pneumonia, two for sepsis, one for peritonitis, and four for other infections. In the azathioprine group, eight patients were rehospitalized because of infections: three for pneumonia, one for colon perforation and sepsis, three for systemic viral infections, and one for bacterial sepsis. The risk of developing a severe infection was, respectively, 25 ± 6.3% and 29 ± 8.8% (P = NS).

Four cases of malignancies were observed. In the cyclosporine group, one 18-yr-old woman died of a cerebral lymphoma 4½ yr after transplantation. Two other patients had skin tumors (one had one basal cell carcinoma and the other had multiple basal cell carcinomas), which were removed; both patients are alive and well. In the azathioprine group, one patient had an excised spinal cell carcinoma, and is also alive and well. During the study, the risk of neoplasia was 0.8 per 100 patient-yr in the cyclosporine group and 0.4 in the azathioprine group (P = NS).

**Complications and Adverse Events**

Tremors, hypertrichosis, gingival hyperplasia, and hyperuricemia were more frequent in the cyclosporine group than in the azathioprine group (Table 1). Cardiovascular events (myocardial infarction, heart ischemia, arrhythmias, angina, obliterative peripheral arterial disease) were more frequent, but not significantly so, in the azathioprine group (20.8% versus 10%, P = 0.1); on the contrary, the probability of developing cataracts was higher, but not significantly so, in the cyclosporine group (42.6% versus 24.5%, P = 0.1). The risk of other complications (chronic liver disease, osteoarticular problems, hypertension, diabetes, obesity, hypercholesterolemia) was similar in the two groups. The median duration of hospitalization in the first 3 months was shorter in the cyclosporine group (15 days; range, 11 to 68) than in the azathioprine group (27 days; range, 12 to 60; P < 0.01); the frequency and duration of hospitalization afterward was similar in the two groups.

**TABLE 1. Percentage probability of developing complications in the 10-yr follow-up period**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Cyclosporine</th>
<th>Azathioprine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>81.5</td>
<td>73.9</td>
<td>0.50</td>
</tr>
<tr>
<td>Cataracts</td>
<td>42.6</td>
<td>24.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Severe Infection</td>
<td>25.0</td>
<td>29.2</td>
<td>0.95</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>20.7</td>
<td>19.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Cardiovascular Events</td>
<td>10.0</td>
<td>20.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.0</td>
<td>12.2</td>
<td>0.74</td>
</tr>
<tr>
<td>Osteoarticular Events</td>
<td>9.5</td>
<td>10.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>35.0</td>
<td>5.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>37.1</td>
<td>29.4</td>
<td>0.40</td>
</tr>
<tr>
<td>Tremors</td>
<td>27.2</td>
<td>6.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Gingival Hyperplasia</td>
<td>43.0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>67.6</td>
<td>10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cataracts</td>
<td>6.4</td>
<td>5.0</td>
<td>0.64</td>
</tr>
</tbody>
</table>

a Includes heart ischemia, angina, phlebitis, myocardial infarction, and severe peripheral vasculopathy.
b Includes bone fractures, aseptic necrosis of femoral heads, and tendon rupture.

c One lymphoma and two skin cancers in the cyclosporine group; one skin cancer in the azathioprine group.

**DISCUSSION**

Three controlled trials have reported better short-term graft survival in cyclosporine- than in azathioprine-treated patients (1–3); another study did not find any difference in graft survival between patients given cyclosporine and those given azathioprine, steroids, and antilymphocyte globulins (18). However, controlled data on the long-term effects of cyclosporine are scanty. The Multicentre European Trial Group recently reported (19) that 10-yr graft survival was only slightly improved in comparison with azathioprine (35% versus 29%). In that study, cyclosporine was initially given without steroids and a large proportion of patients (40%) was switched to azathioprine and steroids mainly because the protocol required cyclosporine to be abandoned in case of two consecutive rejections. It should also be pointed out that when the Multicentre European Trial was started, accurate assays for measuring blood cyclosporine levels were not available, and there was little information about the pharmacokinetics and the side-effects of this drug. In our study, cyclosporine was given in combination with steroids; any switch to azathioprine was made only in the case of severe nephrotoxicity, and blood cyclosporine levels were monitored from the beginning. In the study presented here, the graft survival probability at 10 yr was more than 20% better in the cyclosporine- than in the azathioprine-treated patients, in spite of the fact that more children and women, who seem to have an increased risk of graft loss (20,21), were randomized to cyclosporine. The graft half-life in the cyclosporine group was 15.4 yr, almost double the 7.8 yr reported in the University of California at Los Angeles registry (12) and one-third
longer than in the azathioprine group. The better results observed in the cyclosporine-treated group may be first accounted for by the significantly lower number of acute early rejections: acute rejection not only affects the results of transplantation in the short term, but is by far the most important covariate associated with poor long-term cadaveric graft survival (22-24). Moreover, in our trial, the patients randomized to azathioprine had a higher cumulative number of late rejections.

There has been much concern about the long-term nephrotoxicity of cyclosporine, and it is well known that the use of high doses of cyclosporine may cause irreversible renal failure even in patients with nonrenal diseases (8,9,25). To prevent long-term toxicity, some investigators have therefore proposed switching patients from cyclosporine to azathioprine (26-28). However, although some studies have reported excellent results after such a switch (28), others have pointed out that it may increase the risk of irreversible chronic rejection (29-31). In the large trial of the Collaborative Transplant Study, the patients who discontinued cyclosporine during the first yr after transplantation had a 5-yr graft-survival rate that was 11% lower than that of the patients who continued treatment with cyclosporine (32). In this study, conversion to azathioprine resulted in irreversible rejection or death in almost one-third of cases. On the other hand, renal failure is not an inevitable fate for cyclosporine-treated patients. A number of studies have shown that the careful handling of cyclosporine may allow long-term stable renal function in kidney transplant recipients (33-37). In this controlled study, we found that the slope of creatinine clearance rate between the first and the tenth yr was similar in both groups of patients, although the mean levels of creatinine clearance rate were always better in the azathioprine-treated patients at all time points.

The risk of severe infections, hepatic complications, diabetes, hypertension, and osteoarticular problems was similar in the two groups. During the long-term follow-up, there was a trend toward an increased number of cataracts in the cyclosporine group (in spite of the reduced dose of prednisone), thus confirming in man the cataractogenic effect of cyclosporine that has been reported in rats (38). On the other hand, there was a trend toward an increased risk for cardiovascular events in the patients in the azathioprine group, possibly as a consequence of the higher steroid doses. The risk of neoplasia (all but one being skin tumors) was relatively low in both groups.

In conclusion, this randomized study shows that long-term cyclosporine treatment allows better 10-yr graft survival than azathioprine does in cadaveric renal transplants, with a similar attrition of renal function and a similar incidence of extrarenal side effects. These satisfying results were obtained despite the fact that we had had no experience with cyclosporine before this trial and that high doses were initially adopted.

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