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LONG-TERM USE OF CYCLOSPORINE IN LIVER RECIPIENTS

REDUCTION OF DOSAGES IN THE FIRST YEAR TO AVOID NEPHROTOXICITY[1,2]

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Cyclosporine is a potent immunosuppressive drug, which has dose-related nephrotoxicity. In renal transplantation, the differentiation between rejection and toxicity is difficult and even with the aid of blood levels of the drug, it may be difficult to establish a chronic maintenance dose. Long-term survivors after liver transplantation can provide modes with which to establish maintenance doses, as these are dictated by nephrotoxicity in these patients. Twenty-nine liver transplant patients who survived one year or more were followed for changes in their cyclosporine doses. Daily oral cyclosporine dose, BUN, serum creatinine and bilirubin were monitored. The reductions in cyclosporine were dictated almost entirely by the findings of nephrotoxicity.

Cyclosporine is a potent immunosuppressive agent that has dose-related nephrotoxicity (1–3). In renal transplantation, differentiation between rejection and drug toxicity is often difficult. Even with the aid of blood levels of the drug it may be difficult to establish a chronic maintenance dose. Long-term survivors after liver transplantation can provide ideal models with which to establish maintenance doses of cyclosporine, because these are dictated by nephrotoxicity.

MATERIALS AND METHODS

Case materials. From March, 1980 to May 1982, 67 patients received orthotopic liver allografts under cyclosporine–low-dose-steroid therapy. Forty-one of the 67 recipients lived one year or longer as of May, 1983 (one-year actual survival of 61%). One patient who was dying of recurrent cholangiocarcinoma was excluded from analysis because immunosuppression had been stopped.

TABLE 1. Indications for transplantation in adult patients (≥19 years) from March 1980 to May 1982

Indications	No.
Chronic aggressive hepatitis	14
Malignancy[a]	9
Primary biliary cirrhosis	6
Secondary biliary cirrhosis	4
2 trauma	
1 Caroli	
1 choledochal cyst	
Sclerosing cholangitis	3
α-1-antitrypsin deficiency	2
Budd-Chiari syndrome	2
Adenomatosis[a]	1
Total	41

[a] One patient in each group had had previous right hepatic trisegmentectomy (at 1 and 4½ years earlier). At transplantation, the regenerated left-lateral segment was replaced with a whole liver.

Indications for orthotopic liver transplantation are shown in Tables 1 and 2. Common indications in adults were chronic aggressive hepatitis, primary liver malignancy, and primary biliary cirrhosis. Common diagnoses in children were biliary atresia and alpha-1-antitrypsin deficiency disease.

Twenty-six of the 41 one-year survivors were adults over the age of 18 years, weighing more than 40 kg; 6 were school children and adolescents aged 7–17, weighing 21–40 kg; and nine were infants and preschool children under the age of 7 years and below the weight of 20 kg.

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Cyclosporine dose. All patients received their first doses of cyclosporine several hours before transplantation, either 17.5 mg/kg by mouth or 5 mg/kg i.v. (4). After transplantation, 5–6 mg/kg/day of cyclosporine was given i.v. in two divided doses until the oral dose was tolerated. Within a few days 17.5 mg/kg/day of cyclosporine in two divided doses was administered orally. The dose of cyclosporine was reduced in the presence of renal failure soon after transplant, or the dose was adjusted to maintain near-normal BUN (less than 40 mg%) and serum creatinine (less than 2 mg%).

Steroid dose. In adults 1 g methylprednisolone was given i.v. intraoperatively. After the operation a 5-day burst of prednisone or methylprednisolone was begun at 200 mg/day, and the dose was reduced by daily increments of 40 mg to an initial daily maintenance dose of 20 mg/day (*4*).

In children 250 mg or 500 mg of methylprednisolone was given i.v. intraoperatively. After the operation, a 5-day burst of prednisone or methylprednisolone was begun at 100 mg/day, and the dose was reduced by daily increments of 20 mg to an initial daily maintenance dose of 10 mg/day. Further downward adjustment of steroid dosage was made in smaller children and infants (*4*).

In case of acute rejection a bolus of i.v. steroid therapy or a 5-day burst of prednisone, or both, was repeated.

TABLE 2. Indications for transplantation in pediatric patients (≤18 years) from March 1980 to May, 1982

Indications	No.
Biliary atresia[a]	11
α-1-antitrypsin deficiency[b]	4
Chronic aggressive hepatitis	2
Byler's disease[c]	2
Secondary biliary cirrhosis[d]	1
Budd-Chiari syndrome	1
Neonatal hepatitis	1
Subacute Wilson's disease[b]	1
Tyrosinemia[b]	1
Type I glycogen storage disease[b]	1
Sea-blue histiocyte syndrome[b]	1
Total	26

[a] Two had Alagille's syndrome.

[b] Inborn errors of metabolism; the children with tyrosinemia and sea-blue histiocyte syndrome had incidental hepatomas in their cirrhotic livers.

[c] Diagnosis equivocal in one case.

[d] Choledochal cyst with multiple operations.

RESULTS

Daily oral cyclosporine dose, BUN, serum creatinine, and total bilirubin before liver transplantation, at 1, 3, 6, 9, and 12 months are shown in Tables 3, 4, and 5. The daily oral dose of cyclosporine at 12 months after liver transplantation to avoid

TABLE 3. Daily oral cyclosporine dose, BUN, serum creatinine, and total bilirubin before transplant, at 1, 3, 6, 9, and 12 months among 25 adult recipients (age ≥19 years old and body weight ≥41 kg)

	Pre-TX[a]	1 Month	3 Months	6 Months	9 Months	12 Months
Cyclosporine (mg/kg/day p.o.)	17.5	12.5±4.3	10.8±6.7	8.2±3.6	7.6±3.5	6.7±2.2
BUN mg%	18.1±19.8	37.3±28.8	36.9±16.6	33.9±11.1	36.3±12.1	30.6±11.7
Creatinine mg%	1.2±0.8	2.2±2.2	1.5±0.7	1.6±0.6	1.9±0.7	1.6±0.4
Bilirubin mg%	9.9±12.4	3.6±3.2	3.0±5.7	1.3±1.7	2.6±5.8[b]	1.4±7.2
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)

[a] Before transplantation.

[b] High values were influenced by two patients, one of whom had chronic rejection and another of whom had biliary obstruction resulting from recurrent cancer.

TABLE 4. Daily oral cyclosporine dose, BUN, serum creatinine, and total bilirubin before transplant, at 1, 3, 6, 9, and 12 months among 6 school-aged pediatric recipients (age between 7 and 18 years old, and body weight between 21 and 40 kg)

	Pre-TX[a]	1 Month	3 Months	6 Months	9 Months	12 Months
Cyclosporine (mg/kg p.o.)	17.5	12.11±3.1	12.7±5.6	10.5±2.8	8.9±5.6	9.8±2.7
BUN mg%	32.5±36.2	32.0±14.8	27.7±12.0	26.8±13.6	24.0±13.5	25.5±21.9
Creatinine mg%	1.6±1.6	1.0±0.9	0.8±0.2	0.9±0.4	1.0±0.4	0.8±0.4
Bilirubin mg%	19.0±15.8	3.8±4.8	1.5±1.2	1.1±0.7	1.0±0.96	1.0±0.9
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)

[a] Before transplantation.

TABLE 5. Daily oral cyclosporine dose, BUN, serum creatinine, and total bilirubin before transplant, at 1, 3, 6, 9, and 12 months among 9 preschool-aged pediatric recipients (age ≤6 years old and body weight ≤20 kg)

	Pre-TX[a]	1 Month	3 Months	6 Months	9 Months	12 Months
Cyclosporine (mg/kg/day p.o.)	17.5	17.1±3.9	17.8±5.6	14.7±5.3	12.1±3.8	11.1±2.2
BUN mg%	14.4±6.6	18.1±13.5	15.7±4.7	17.3±5.3	23.9±12.7	20.7±7.7
Creatinine mg%	0.7±0.6	0.4±0.2	0.4±0.2	0.5±0.2	0.5±0.2	0.5±0.1
Bilirubin mg%	11.7±11.6	3.6±5.6	1.2±1.2	0.6±0.3	0.6±0.3	0.5±0.2
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)

[a] Before transplantation.

nephrotoxicity was 6.7 mg±2.2 mg/kg/day for adults, 9.8±2.7 mg/kg/day for school children and adolescents, and 11.05 ± 2.2. mg/kg/day for infants and preschool children. Pediatric patients could tolerate larger doses of cyclosporine than adult patients.

DISCUSSION

Acute and chronic nephrotoxicity of cyclosporine has been a clinical problem since the introduction of this potent immunosuppressive agent to organ transplantation. Clinical differentiation of nephrotoxicity of cyclosporine from renal graft rejection is quite important but often difficult even with the measurement of drug blood levels. Despite the need, no dosage guide has been established for long-term use of cyclosporine to avoid nephrotoxicity. Survivors of extrarenal organ transplantation, such as liver transplantation, provide this information, because renal functions of these patients have mostly been dictated by the nephrotoxicity of cyclosporine. The dosage guide provided by this study should be useful in long-term management of patients with cyclosporine.

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