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Hepatic Homograft Survival in Pediatric Orthotopic Liver Transplantation with Cyclosporine and Steroids

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CYCLOSPORINE (CsA) used with steroids has been a major influence in the improved survival of patients undergoing orthotopic liver transplantation. The overall results of patient survival have been published elsewhere.[1,2] Part of the increased survival rate is dependent on retransplantation for homograft failure. We report our experience of patient and homograft survival as well as major causes for graft failure.

MATERIALS AND METHODS

From May 11, 1981, to March 7, 1983, 43 patients ranging in age from 7½ months to 18 years received 57 orthotopic liver homografts. Table 1 lists the indications for transplantation. Patients reported here have been assigned OT (orthotopic transplant) numbers, which allows one to follow and compare the course of any one patient in previous or subsequent publications. Details of patient selection and immunosuppression have been described in detail elsewhere.[1-3] Briefly, patients were given oral CsA (17.5 mg/kg) or an intravenous infusion of CsA (5 mg/kg) a few hours preoperatively. Intravenous CsA was continued at 5 mg/kg/day, divided twice daily, until oral CsA could be begun at 17.5 mg/kg/day, divided twice daily. Most pediatric patients were given a burst of steroids beginning the day of surgery (100 mg methylprednisolone) and rapidly tapered to a baseline dose (20 mg/day of prednisone) 4–5 days postoperatively. This baseline steroid dose was further decreased pending the patient's clinical course.

If clinical signs of rejection appeared, the immunosuppression regimen was modified. Initially, a single bolus of hydrocortisone (500–1000 mg) was given intravenously. If the patient showed only moderate improvement, a cycle of prednisone similar to that given immediately postoperatively was also begun. In addition, CsA doses were occasionally increased, monitoring clinical and laboratory evidence for nephrotoxicity. Whole blood CsA levels were measured by high-pressure liquid chromatography[4] in patients transplanted since January 1983, and CsA doses were adjusted to achieve trough levels of 100–400 ng/ml.

Graft failures occurred when irreversible and progressive hepatic injury was noted by increases in bilirubin and hepatocellular and canalicular enzymes as well as worsening prothrombin time.

RESULTS AND DISCUSSION

From 5/11/81 to 3/7/83, 43 pediatric patients received 57 hepatic homografts. Overall patient survival to 3/7/83 is 63% (27/43). Thirteen patients (30%) received multiple transplants; 12 patients received two homografts, and 1 patient received three homografts. The overall patient survival of retransplanted patient is 38% (5/13).

Twenty-four overt graft failures occurred in the 57 homografts (42%). Of the 16 patients who died, transplantation in 6 patients took place while the patient was moribund, and the patient expired shortly after surgery. Graft function was assessed shortly prior to death. Those six grafts are not included in graft failures.

Causes of graft failure and contributing causes of graft failure are listed in Table 2. Although the primary cause of graft failure is given, other factors often contributed to graft injury. At times it was difficult to determine which was the dominant factor responsible for graft failure. The most prominent pathological event found in the graft at retransplantation or autopsy helped determine the major factor. Infarction, rejection, vascular accidents, and infection were the major causes of graft failures (Table 3).

Infarction

Hepatic infarction accounted for the loss of eight grafts (33%). All but two of these grafts never had adequate function and were marked by an immediate and continued postoperative enzyme elevation, often in the thousands. Bili-

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Table 1. Indications for Pediatric Liver Transplantation

Biliary atresia	18
Metabolic	
Alpha-1-antitrypsin deficiency	7
Glycogen storage Disease I	1
Hereditary tyrosinemia	1
Wilson's disease	2
Sea blue histiocyte	1
Biliary hypoplasia	4
Chronic active hepatitis	3
Familial cholestasis	3
Neonatal hepatitis	1
Biliary obstruction	1
Benign liver tumor	1
Total	43

rubin also rose, and clotting studies worsened. Death occurred if retransplantation did not occur within 72–96 hr. Reasons for graft infarction were not clear because vessels were all patent at retransplantation or autopsy. Possible factors for infarction might include transplantation of an already injured graft or damage to the graft during harvesting, transport, or implantation. An example of the latter might be OT 279B, who suffered an intraoperative cardiac arrest. The graft never functioned well.

Two patients, OT 232 and OT 240, had a delayed onset of massive hepatic infarction. OT 232 had an absent inferior vena cava. Each had initial good function postoperatively but suffered subsequent fulminant hepatic necrosis and death at 12 and 10 days, respectively. Both grafts had patent vascular anastomoses at postmortem examination. Both patients, however, had preformed T-cell warm antibodies directed against the graft. Whether acute rejection was contributory to the infarction is purely speculative.

Table 3. Status of Surviving Grafts

Discharged survivors*	26
Bilirubin < 1.5 mg/dl	24
SGOT < 100 IU	25
Status	
Well	24
Chronic rejection	1
Mild rejection	1

*OT 246, not included, recently underwent a third transplant and is still hospitalized.

Rejection

Rejection occurred as a major cause of graft failure in 29% (7/24) of grafts. In addition, it was a contributing factor in the failure of another 4 grafts. Pathological features of rejection have been described elsewhere.[5–7] In most cases, rejection was manifested by fever, malaise, hepatomegaly with induration of the graft, ascites, and vague abdominal discomfort. Bilirubin increased and canalicular enzymes increased, usually out of proportion to the hepatocellular enzymes. Generally an ominous prognostic feature has been the disappearance of bile ducts within the portal triads.[2,7] Clinically, rejection mimicked other disorders, especially biliary tract obstruction and portal vein occlusion. If the patient did not respond to specific therapy directed toward rejection, the pathological process could be determined with certainty only with specific investigations such as cholangiography and angiography, as well as biopsy. In addition, these clinical entities may not be exclusive of each other, and it is at least theoretically possible that they may contribute to one another. Such an example might be decreased hepatic blood flow during rejection

Table 2. Causes of Graft Failure

Failure (No.) (*N* = 24)	Major Cause	Contributing Cause
Hepatic infarction (8)	OT 265, 271A, 271B, 240, 232,284A, 203A, 279B	—
Rejection (7)	OT 216, 214A, 203B, 266A, 229A, 246A, 250A	OT 232, 214B, 240, 191
Vascular accident (5)	OT 220, 259A, 273A, 267, 214B	OT 232, 259B, 266A
Infection (4)	OT 201, 191, 259B, 279A	OT 259A, 266A, 246A

causing vascular thrombosis and/or infection.[8]

OT 266A had clinical and pathological evidence for chronic rejection while on 18 mg/kg/day of CsA. Prior to retransplantation, CsA kinetics studies demonstrated poor oral absorption at that dose. Retransplantation occurred 57 days after the initial transplant. Pathology of the initial graft demonstrated severe rejection and a branch hepatic artery thrombosis. Cyclosporine was increased to 29 mg/kg/day, achieving adequate blood CsA levels, possibly preserving good function of the second graft. No nephrotoxicity was noted. This patient demonstrated the possible interplay of several pathological processes as well as the possible potential value o measuring CsA levels. In addition, this patien was representative of many of our patient who received higher than the standard CsA dose and appeared to tolerate it without overt nephrotoxicity.

Vascular Accidents

Vascular complications accounted for the loss of 5 (21%) grafts. OT 220A had no portal vein found at transplant, and the portal anastomosis was made to the recipient's vena cava. The graft failed from portoprival flow. OT 259A suffered both portal vein thrombosis and hepatic artery thrombosis; OT 267 thrombosed the hepatic artery; OT 273A had a

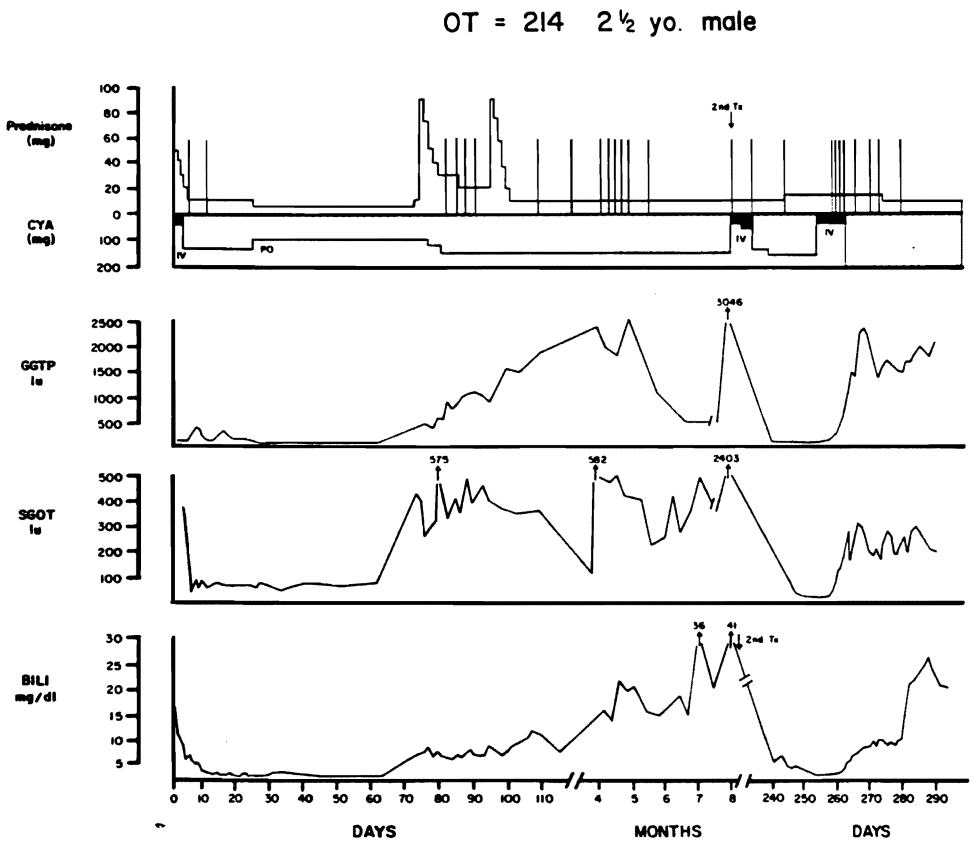

Fig. 1. Clinical course of OT 214. Note the late onset of rejection marked by rises in SGOT, GGTP, and bilirubin. Rejection persisted despite aggressive immunosuppression, culminating in retransplantation on day 241. The course of the second transplant was marked by rises in the same laboratory studies. Steroid boluses did not alter the course. Postmortem examination confirmed the premortem diagnosis of portal vein thrombosis. Vertical bars during steroid therapy indicate large boluses of i.v. steroid. The CsA graph indicates i.v. dosing by the solid bar and oral dosing by the open bar.

thrombosis of the portal vein and inferior vena cava; and OT 214B had a thrombosed portal vein. Vascular complications may have been contributory in the failure of another 3 cases.

The course of OT 214A and B is depicted in Fig. 1. The first graft was lost to rejection, and the second to a portal vein thrombosis. This patient was unusual because unrelenting rejection occurred several weeks after achieving normal liver functions—later than most patients. Despite continued high-dose steroids, the course of rejection was unaltered. The patient became increasingly debilitated with high-dose immunosuppression. The clinical course and laboratory findings of rejection and portal vein thrombosis were similar. We have since changed our approach to patients with chronic rejection. Once it is determined that rejection is irreversible through lack of response to increased immune suppression and pathological evidence, retransplantation is considered earlier. The patient's immune suppression is decreased to avoid overimmunosuppression. The surgery is often easier because vital structures already have been skeletonized and the patient is not debilitated from chronic overimmunosuppression.

Infection

Infection leading to graft failure occurred in 4 (17%) patients and was a contributing factor in another 3 losses. In patients OT 201 and OT 279A, biliary tract reconstruction may have been the initial inciting event, leading to biliary sepsis and graft failure. The second liver of OT 259B was grafted to vessels already infected with candida and *Pseudomonas aeruginosa*. OT 191 emphasized Starzl's concept of septic hepatic gangrene.[5] The patient had a large fungal abscess. The homograft injured from rejection or vascular insult is much more susceptible to infection than one not injured.

Hepatic homograft loss was a frequent complication of transplantation. Acute hepatic infarction, rejection (despite the use of CsA and steroids), vascular accidents, and infection were primary causes of graft failure. Early retransplantation may be beneficial in preventing patient death with initial graft loss.

Surviving Grafts

The current status of 27 surviving patients is listed in Table 3. One patient recently underwent a third transplant (not in the time frame discussed above) and will not be included in the following discussion. Of the 26 remaining survivors, 24 (92%) have bilirubins under 1.5 mg/dl. Of the 2 patients with elevated bilirubins, OT 206 has chronic rejection and may require retransplantation; OT 237 has mild rejection due to drastic lowering of immunosuppression because of an intestinal lymphoma. OT 206 is the only patient who has an SGOT of >100 IU. Daily prednisone dose averages 0.4 mg/kg/day, and the mean CsA dose is 15.5 mg/kg/day. Cyclosporine doses in patients transplanted prior to 9/82 average only 10 mg/kg/day. Patients transplanted subsequently, however, have an average dose of 25.6 mg/kg/day. Generally, this dose is able to be decreased to 8–10 mg/kg/day within the first postoperative year.[9] It appears, therefore, that the vast majority of surviving grafts have excellent function.

CONCLUSIONS

Hepatic homograft failures occur frequently (42%) and remain a major cause of morbidity and mortality in pediatric liver transplant patients. Graft infarction (33%), rejection despite the use of CsA and steroids (29%), vascular accidents (21%), and infection (17%) are major causes of graft failure. Attempts to control rejection may involve using higher doses of CsA than previously accepted, and children may tolerate larger oral doses with little nephrotoxicity. Despite a 30% retransplantation rate, 92% of surviving grafts are associated with bilirubins of <1.5 mg/dl, indicating excellent function of surviving grafts.

ADDENDUM

Since submission of this manuscript, OT 206 underwent successful retransplantation for chronic rejection. Her bilirubin and enzymes are within normal limits.

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