RANDOMIZED CONTROLLED TRIAL OF ORAL GANCICLOVIR VERSUS ORAL ACYCLOVIR AFTER INDUCTION WITH INTRAVENOUS GANCICLOVIR FOR LONG-TERM PROPHYLAXIS OF CYTOMEGALOVIRUS DISEASE IN CYTOMEGALOVIRUS-SEROPOSITIVE LIVER TRANSPLANT RECIPIENTS

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Background. **Without effective antiviral prophylaxis, cytomegalovirus (CMV) disease is a common cause of morbidity and mortality after liver transplantation. In this randomized, controlled trial, we compared the efficacy and safety of oral ganciclovir with oral acyclovir after induction with intravenous (IV) ganciclovir for long-term prophylaxis of CMV disease in CMV-seropositive liver transplant recipients.**

Methods. **Patients were initially administered IV ganciclovir at a dose of 6 mg/kg per day from day 1 to day 14 after transplantation followed by either oral ganciclovir (1 g every 8 hr) or oral acyclovir (800 mg every 6 hr) from day 15 to day 100 after transplantation.**

Results. **CMV disease occurred in only 1 of 110 patients (0.9%) receiving ganciclovir compared with 8 of 109 patients (7.3%) receiving acyclovir within the first year after transplantation ($P=0.019$). There was one case of CMV colitis in the ganciclovir group, whereas four cases of CMV syndrome, three cases of CMV pneumonia, and one case of CMV hepatitis developed in the acyclovir group. The only death from CMV disease occurred in an acyclovir-treated patient with CMV pneumonia. Both oral ganciclovir and oral acyclovir were generally well tolerated. Reversible leukopenia (decline in white blood cell count to $<3.0\times10^9$/L) was more common with oral ganciclovir (38/110 patients, 35%) than with oral acyclovir (20/109 patients, 18%) ($P=0.009$). The emergence of ganciclovir-resistant strains of CMV was not found during the study.**

Conclusions. **A prophylactic regimen of 2 weeks of IV ganciclovir followed by an additional 12 weeks of oral ganciclovir is superior to a similar regimen of IV ganciclovir followed by oral acyclovir and almost completely eliminates CMV disease after liver transplantation. This superior protection against CMV disease extends up to 1 year after transplantation and is not associated with ganciclovir resistance.**

Cytomegalovirus (CMV) disease can now be successfully prevented in many liver transplant recipients because of effective prophylactic strategies (*1*). On the basis of the results of a randomized, double-blind trial, oral ganciclovir is commonly used for prevention of CMV disease after liver transplantation (*2*). In this trial, the incidence of CMV disease was reduced significantly from 19% in a group of patients receiving placebo to 5% in a group of patients receiving oral ganciclovir for 3 months after transplantation. Nonetheless, this study had certain limitations. First, the study excluded patients unable to take oral medications by day 10 after transplantation; such patients may be at increased risk for CMV disease. Second, this study used a placebo in the control group despite the availability of other agents (acyclovir, CMV hyperimmune globulin, and intravenous [IV] ganciclovir) that have been shown to be effective for prophylaxis of CMV disease (*1*). Indeed, a regimen of IV ganciclovir for 2 weeks followed by oral acyclovir for 12 weeks was associated with only a 10% incidence of CMV disease and minimal toxicity in two separate trials involving liver transplant recipients (*3*, *4*). At the University of California–Los Angeles (UCLA) Medical Center, this regimen has been the standard approach for CMV prophylaxis for CMV-seropositive liver transplant patients. Thus, after initial therapy with 2 weeks of IV ganciclovir, we undertook this study to compare the efficacy and safety of oral ganciclovir with oral acyclovir for prevention of CMV disease in CMV-seropositive liver transplant recipients.

PATIENTS AND METHODS

Patients undergoing orthotopic liver transplantation at the UCLA Medical Center were enrolled in the study if they were seropositive for CMV antibody before transplant and demonstrated no clinical symptoms or signs of proven CMV disease. Informed consent approved by the UCLA Human Subject Protection Committee was obtained from each patient or responsible relative. The operative procedures and posttransplant management used in liver transplant recipients at the UCLA Medical Center have been previously published (*5*, *6*).

Patients were assigned randomly to receive prophylaxis with either oral ganciclovir or oral acyclovir. All patients initially received IV ganciclovir through a central IV catheter at a dose of 6 mg/kg of body weight once per day, starting on the first day after the transplant and continuing through day 14 after transplant. Patients then received either oral ganciclovir, at a dose of 1 g every 8 hr, or oral acyclovir, at a dose of 800 mg every 6 hr, until day 100 after transplant. If a patient was unable to take oral medications, IV ganciclovir (6 mg/kg of body weight once per day) or IV acyclovir (10 mg/kg of body weight every 8 hr) was administered in place of oral therapy. The dosage of ganciclovir or acyclovir was adjusted for impaired renal function according to previously published guidelines (*2–4*).

The CMV antibody status of patients and liver donors was determined by latex agglutination (CMV SCAN, Becton Dickinson, Sparks, MD). Patients were evaluated for CMV viremia and disease whenever any of the following symptoms, signs, or laboratory abnormalities developed: fever (temperature $\geq$38°C), leukopenia (leukocyte count $<3.0\times10^9$/L), thrombocytopenia (platelet count $<75\times10^9$/L), generalized wasting, liver graft dysfunction, gastrointestinal complaints (nausea, vomiting, abdominal pain, diarrhea, and bleeding), dyspnea and pulmonary infiltrates on chest roentgenogram, or

Supported in part by a research grant from Roche Laboratories, Inc.

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Received 1 April 2002. Accepted 29 July 2002.

DOI: 10.1097/01.TP.0000040601.60276.96

any other organ dysfunction suggestive of CMV disease. For patients with suspected CMV disease, blood for quantitation of CMV DNA (Digene Hybrid Capture System, Digene Corporation, Gaithersburg, MD) and CMV culture and urine for CMV culture were obtained. Whenever indicated by clinical findings, viral cultures of bronchoalveolar lavage, biopsy material, or any suspicious viral lesion were performed. Biopsy material and bronchoalveolar lavage were examined histologically for typical viral inclusions and stained immunohistochemically by indirect immunofluorescence using CMV monoclonal antibodies. Complete blood counts with differential white blood cell counts (WBCs) and platelet counts, blood urea nitrogen levels, serum creatinine and electrolyte determinations, and liver function studies (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels) were obtained at study entry, at least weekly during periods of hospitalization, and at each posttransplant clinic visit to assess for adverse effects related to the study drugs.

CMV syndrome was defined as persistent fever (temperature >38°C for >2 days) and wasting, with or without leukopenia (WBC$<3.5\times10^9$/L) and thrombocytopenia (platelet count $<100{,}000\times10^9$/L), which could not be attributed to other causes in a patient with CMV viremia. CMV disease of the liver or gastrointestinal tract was diagnosed by finding histologic or culture evidence of CMV in a biopsy of the liver or gastrointestinal tract in a patient with liver dysfunction or gastrointestinal symptoms not explainable by other causes. CMV pneumonia was diagnosed by demonstrating the presence of CMV in a bronchoalveolar lavage or lung tissue from a patient with tachypnea, hypoxemia, fever, and interstitial pulmonary infiltrates not explainable by other obvious causes.

Fisher's exact two-tail test was used to compare differences in proportions. Comparisons of times to specific events were performed by using the Kaplan-Meier method and the log-rank test. All patients were included in the efficacy analysis (intent-to-treat analysis) and the safety analysis. Patients were followed until 1 year after transplantation or time of death.

RESULTS

A total of 219 patients were enrolled in the study; 109 patients were randomized to receive oral acyclovir and 110 patients to receive oral ganciclovir (Table 1). The characteristics of the patients in the two study groups were similar and are summarized in Table 1.

Recipients of oral ganciclovir demonstrated a significantly lower incidence of CMV disease than recipients of oral acyclovir (Table 2, Figure 1). Eight of 109 patients (7.3%) receiving acyclovir but only 1 of 110 patients (0.9%) receiving ganciclovir developed CMV disease ($P=0.019$). There were four cases of CMV syndrome, three cases of CMV pneumonia, and one case of CMV hepatitis in the acyclovir group. The median time of onset of CMV disease in the acyclovir group was 131 days after transplant (range, 47–226). The only case of CMV disease in the ganciclovir group was a patient with CMV colitis, which developed on day 132 after transplantation when the patient was no longer taking oral ganciclovir. Seven of the eight acyclovir-treated patients with CMV disease improved after treatment with IV ganciclovir. One acyclovir-treated patient with CMV pneumonia and viremia on day 171 after transplantation died despite treatment with IV ganciclovir followed by foscarnet. The ganciclovir-treated patient with CMV colitis improved spontaneously without any additional antiviral therapy.

There were no cases of herpes simplex virus or Epstein-Barr virus disease diagnosed during the study. Four ganciclovir-treated patients developed localized varicella-zoster virus disease between days 150 and 292 after transplant, which was treated successfully with acyclovir. No cases of varicella-zoster virus disease occurred in the acyclovir group. One acyclovir-treated patient and one ganciclovir-treated patient each demonstrated adenovirus isolated from respiratory secretions, but neither patient showed any evidence of viral disease.

No clinical adverse events could be attributed to either study drug. Leukopenia (WBC$<3.0\times10^9$/L) occurred in 38 of 110 ganciclovir-treated patients (35%) and in 20 of 109 acyclovir-treated patients (18%) ($P=0.009$). Severe leukopenia (WBC$<1.0\times10^9$/L) developed in five ganciclovir-treated patients (5%) and in one acyclovir-treated patient (1%). Sixteen ganciclovir-treated patients (15%), but none of the acyclovir-treated patients, had their CMV prophylactic drug discontinued as a result of leukopenia ($P<0.001$). Two ganciclovir-treated patients who developed bone marrow hypoplasia associated with graft-versus-host disease, but unrelated to ganciclovir, did not resume prophylactic ganciclovir. A third ganciclovir-treated patient who developed leukopenia was switched to oral acyclovir. The other 13 ganciclovir-treated patients with leukopenia causing discontinuation of the study drug resumed prophylactic oral ganciclovir at the original dose (1 g every 8 hr) when the leukopenia resolved. Granulocyte colony-stimulating factor was used for treatment of leukopenia in 17 ganciclovir-treated patients (15%) and in six acyclovir-treated patients (6%) ($P=0.026$). There was no increased incidence of infections associated with these episodes of leukopenia.

The number of patients who developed thrombocytopenia (decline in platelet count to $<100{,}000\times10^9$/L after transplantation) was similar in the ganciclovir (23/110, 21%) and acyclovir (16/109, 15%) groups. Severe thrombocytopenia (decline in platelet count to $<20{,}000\times10^9$/L after transplantation) occurred in four ganciclovir-treated patients (4%) and in four acyclovir-treated patients (4%). Two ganciclovir-treated patients and one acyclovir-treated patient had the study drug temporarily stopped because of thrombocytopenia. These patients resumed the study drug after the thrombocytopenia resolved. An increase in serum creatinine concentration (≥1.5 mg/dL) during administration of the study drug after transplantation occurred in 35 of 110 patients (32%) receiving ganciclovir and in 41 of 109 patients (38%) receiving acyclovir. However, no cases of renal dysfunction could be attributed to either ganciclovir or acyclovir, and no patients were removed from the study because of renal failure. There were no significant differences in liver function tests between the ganciclovir- and acyclovir-treated patients.

Survival of patients at 1 year after transplant was similar in the ganciclovir group (89/110, 81%) and in the acyclovir group (93/109, 85%). The causes of death in the 21 ganciclovir-treated patients who died within 1 year after transplantation were liver graft failure (five cases), hemorrhage (four cases), infection (three cases), cardiovascular disease (three cases), pulmonary embolus (two cases), graft-versus-host disease (two cases), respiratory failure (one case), and hepatocellular carcinoma (one case). Similarly, the causes of death in 16 acyclovir-treated patients were liver graft failure (six cases), infection (five cases), hemorrhage (two cases), cardiovascular disease (one case), pulmonary embolus (one case), and central pontine myelinolysis (one case). The only death associated with CMV disease occurred in an acyclovir-treated

TABLE 1. Patients characteristics

Characteristic	Oral acyclovir	Oral ganciclovir
No. of patients	109	110
Median age (range), yrs	51 (7–71)	51 (7–78)
Gender N (%)		
Male	58 (53%)	58 (53%)
Female	51 (47%)	52 (47%)
Underlying disease, N (%)		
Chronic hepatitis C	31 (28%)	30 (27%)
Chronic hepatitis B	15 (14%)	11 (10%)
Alcoholic liver disease	9 (8%)	15 (14%)
Alcoholic liver disease plus chronic hepatitis B or C	19 (17%)	14 (13%)
Cryptogenic cirrhosis	5 (5%)	14 (13%)
Primary biliary cirrhosis	3 (3%)	10 (9%)
Sclerosing cholangitis	5 (5%)	4 (3%)
Autoimmune liver disease	4 (3%)	3 (3%)
Fulminant hepatic failure	8 (7%)	4 (3%)
Wilson's disease	3 (3%)	2 (2%)
Budd-Chiari syndrome	2 (2%)	0
Other[a]	5 (5%)	3 (3%)
Concomitant hepatocellular carcinoma	10 (9%)	12 (11%)
United Network Organ Sharing classification, N (%)		
1 (life support in intensive care)	50 (46%)	42 (38%)
2 (continuous hospitalization)	39 (36%)	37 (34%)
3 (continuous medical care)	20 (18%)	31 (28%)
4 (stable at home)	0	0
Repeat transplant, N (%)	15 (14%)	15 (14%)
Initial immunosuppressive agents, N (%)		
Tacrolimus plus corticosteroids	45 (41%)	48 (44%)
Tacrolimus, mycophenolate, corticosteroids	26 (24%)	26 (24%)
Tacrolimus, azathioprine, corticosteroids	11 (10%)	5 (4%)
Cyclosporine plus corticosteroids	2 (2%)	4 (4%)
Cyclosporine, mycophenolate, corticosteroids	12 (11%)	21 (19%)
Cyclosporine, azathioprine, corticosteroids	13 (12%)	6 (5%)
Patients with rejection, N (%)	37 (34%)	38 (35%)
Treatment for rejection, N (%)		
None	70 (64%)	69 (63%)
Corticosteroids	32 (29%)	33 (30%)
OKT_3 plus corticosteroids	1 (1%)	1 (1%)
Increase baseline immunosuppression	6 (6%)	7 (6%)
CMV serologic status before transplant		
Donor + / recipient +	79 (72%)	81 (74%)
Donor − / recipient +	30 (28%)	29 (26%)

[a] Acyclovir group: polycystic liver disease, Caroli disease, congenital biliary atresia, secondary biliary cirrhosis, and isoniazid toxicity. Ganciclovir group: hepatocellular carcinoma, alpha-1 antitrypsin deficiency, and primary oxalosis.

CMV, cytomegalovirus.

TABLE 2. Incidence of cytomegalovirus disease

Variable	Oral acyclovir	Oral ganciclovir
No. of patients	109	110
Patients with CMV disease, N (%)	8 (7.3%)	1 (0.9%)[a]
Syndrome	4	0
Pneumonia	3	0
Hepatitis	1	0
Colitis	0	1

[a] P value=0.019 versus acyclovir.

patient with CMV pneumonia. No deaths from CMV disease occurred in the ganciclovir group.

DISCUSSION

In this prospective, randomized study, 2 weeks of IV ganciclovir followed by 12 weeks of oral ganciclovir was significantly more effective than 2 weeks of IV ganciclovir followed by 12 weeks of oral acyclovir for CMV prophylaxis in CMV-seropositive liver transplant recipients. Ganciclovir-treated patients demonstrated a 0.9% incidence of CMV disease during the first year after transplant compared with a 7.3% incidence among acyclovir-treated patients. This almost complete elimination of CMV disease after liver transplantation is comparable to what our group observed with 100 days of prophylactic IV ganciclovir (*7*) and is better than a 3.1% incidence of CMV disease reported in CMV-seropositive liver transplant patients receiving only oral ganciclovir for 100 days after liver transplantation (*2*). The latter study excluded patients unable to take oral medications immediately after transplantation, whereas these high-risk patients were included in this study. The 7.3% incidence of CMV disease in the patients administered prophylactic oral acyclovir after 2 weeks of IV ganciclovir in this study is similar to the 9% to

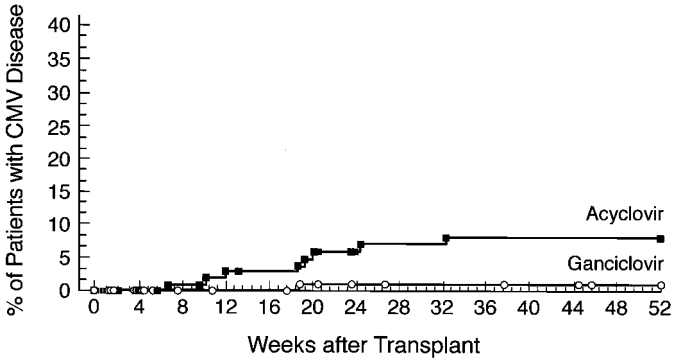

FIGURE 1. Time to development of cytomegalovirus (CMV) disease. Survival distributions of time to development of CMV disease in patients receiving oral acyclovir and oral ganciclovir were defined by using Kaplan-Meier product estimates. For the difference in time of onset of CMV disease between patients receiving oral acyclovir and oral ganciclovir, $P=0.017$.

11% incidence of CMV disease previously reported with this prophylactic regimen in liver transplant recipients (*3*, *4*).

Two other randomized, controlled trials have compared oral ganciclovir with oral acyclovir for CMV prophylaxis in solid-organ transplant patients. In a single-center study involving both CMV-seropositive and CMV-seronegative renal transplant patients receiving induction immunosuppressive therapy with OKT_3, CMV disease occurred in 9 of 39 patients (23%) receiving oral acyclovir but in only 1 of 40 patients (2.5%) receiving oral ganciclovir (*8*). The CMV-seronegative patients in this trial were also administered CMV immune globulin with their acyclovir or ganciclovir prophylaxis. In a multicenter study of CMV-seronegative kidney, liver, or heart transplants with CMV-seropositive donors, all patients initially received IV ganciclovir (5 mg/kg per day) for 5 to 10 days and then either oral ganciclovir (1 g every 8 hr) or low-dose oral acyclovir (400 mg every 8 hr) for an additional 12 weeks (*9*). Symptomatic CMV disease developed in 15 of 77 patients (19%) receiving ganciclovir and in 21 of 78 patients (27%) receiving acyclovir. Tissue invasive disease was less frequent in the ganciclovir group (3/77 patients, 4%) compared with the acyclovir group (10/78 patients, 13%).

Periodic surveillance tests for CMV infection were not performed during this study. Because of logistic and financial reasons, surveillance testing for CMV is not part of standard care of UCLA liver transplant patients. The sponsor of the study did not provide funding for CMV surveillance tests because the primary endpoint of the study was development of CMV disease. Nonetheless, all UCLA liver transplant recipients are instructed to call the transplant center for any fever, chills, gastrointestinal symptoms, shortness of breath, or other sense of ill-feeling. All patients are also closely followed by clinical nurse specialists who maintain frequent contact with patients by phone and during follow-up physician visits. Thus, although cases of asymptomatic CMV infection could have been missed, it is very unlikely that cases of CMV disease were overlooked.

The most common toxicity of ganciclovir is myelosuppression, which has been more common in bone marrow transplant recipients and patients with AIDS than in solid-organ transplant recipients (*10*, *11*). In this study, leukopenia leading to temporary interruption of study drug or the use of granulocyte colony-stimulating factor was more common in patients receiving oral ganciclovir. Nevertheless, the superior effectiveness of oral ganciclovir for prophylaxis of CMV disease was maintained, and there were no serious complications associated with these drug-related episodes of leukopenia that were reversible.

A concern about the use of any antimicrobial agent for prophylaxis is the emergence of resistant organisms. The emergence of ganciclovir-resistant CMV isolates has been reported frequently in patients with AIDS and is associated with the prolonged administration of ganciclovir over many months (*12*). In contrast, the incidence of infection caused by ganciclovir-resistant CMV in solid-organ transplants is much lower, which may be related to the use of ganciclovir prophylaxis for more limited periods (*13*, *14*). Indeed, despite the routine use of ganciclovir and acyclovir for universal prophylaxis in liver transplant patients at UCLA for the last 7 years, ganciclovir resistance has not been a problem.

Another strategy for preventing CMV disease after transplantation is preemptive therapy in asymptomatic patients with a positive surveillance test (culture, antigenemia, and polymerase chain reaction) predictive of CMV disease (*15*). This strategy is designed to limit prophylaxis to high-risk patients and thereby reduce drug costs and the risk for drug toxicity. A clinical trial comparing the relative efficacy, safety, cost, and convenience of preemptive therapy with universal prophylaxis in solid organ transplant patients is needed. Until such a trial is performed, each transplant center will need to decide which strategy is best suited for their patients.

Acknowledgments. The authors thank the following study coordinators for their valuable assistance during this study: Anna Kroeber, RN, Janet Mooney, RN, and Joan Krause, RN. We also thank Dr. David Bruckner and the staff of the UCLA clinical microbiology laboratories for technical assistance, Ed Arriola and the staff of the UCLA pharmacy for administrative assistance, Katharine Fry for preparation of the manuscript, and the UCLA liver transplant physicians and nurses for their help and care of the patients during the study.

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SUCCESSFUL SURGICAL SALVAGE OF PANCREAS ALLOGRAFT

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Background. **Early and late complications related to the pancreas after simultaneous kidney-pancreas transplantation (SKPT) frequently result in graft loss. The authors describe a surgical rescue technique that allows salvage of the pancreatic graft when surgical complications appear after the transplant.**

Methods. **Of 158 patients who underwent SKPT, 7 were identified with posttransplant complications that required surgical salvage of the pancreas allograft. The surgical salvage technique consisted of the following: pancreatoduodenectomy with conversion from whole-pancreas transplant with bladder or enteric diversion to segmental graft with duct injection (three cases) and conversion from whole-pancreas transplant with duct injection (four cases).**

Results. **Five of seven pancreas allografts are still functioning, with a mean follow-up of 28 months (range, 6–42 months).**

Conclusion. **The described surgical treatment may be useful for surgical salvage of the pancreatic allograft, without major impairment of endocrine function.**

Despite the improvements achieved in graft and patient survival, simultaneous pancreas-kidney transplantation (SKPT) is still associated with a high rate of posttransplant complications, such as infections, surgical complications, rejections, and urologic complications. Kelly et al. (*1*) performed the first pancreas transplantation in a human. Subsequently, various techniques have been used to manage pancreatic exocrine secretions such as pancreatic duct occlusion (*2*), whole-pancreas transplantation with bladder diversion (BD) (*3*), and whole-pancreas transplantation with enteric diversion (ED) (*4*, *5*). Segmental pancreas with intraductal injection has been replaced by whole-pancreas transplantation with BD or ED because of pancreatic fibrosis induced by synthetic polymers. This fibrosis is known to induce a reduction, even chronically, in pancreatic endocrine function. In the bladder diversion technique, long-term success was principally limited by urologic complications and readmissions for dehydration. This technique has presented an increased incidence of short- and long-term complications such as recurrent urinary tract infections, hematuria, urethral stricture, chronic intractable metabolic acidosis, and anastomotic leaks (*6*). As previously reported, cystoenteric conversion has been necessary in 20% to 25% of pancreas transplants (*7*). Enteric drainage, introduced in association with segmental graft, is becoming increasingly popular because of the satisfactory results obtained with the cystoenteric conversion (*7*). This technique avoids bladder-specific complications and appears to show a trend toward increased long-term patient survival. For these reasons, the annual number of pancreas transplants for which enteric diversion is used has increased significantly (*8*). Unfortunately, when compared with other abdominal transplants, pancreas transplantation has historically showed the highest incidence of surgical complications, which could jeopardize pancreas graft survival. To improve the rate of pancreas graft surgical salvage, the authors describe a rescue surgical technique in seven patients with early and late surgical complications after SKPT. Furthermore, the authors evaluated whether this technique impaired islet secretory function at least 1 year after the salvage of the pancreas. Of 158 patients with type 1 diabetes and end-stage renal disease who underwent simultaneous kidney transplantation, seven (four women and three men; mean age, 32.7 years; range, 26–46 years) developed severe complications that required surgical salvage of pancreas allograft.

TECHNICAL ASPECTS

The standard technique of organ procurement was used. Selection criteria of the donors were based primarily on the age and pancreas anatomy of the donor. The arterial vascularization of the whole pancreatic graft was reconstructed by interposing an arterial graft of the donor's iliac branching. Systemic venous drainage was obtained by anastomosing the donor's graft portal vein to the recipient iliac vein (six cases). In portal venous drainage, the portal vein of the allograft was

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Received 19 April 2002. Revision requested 14 June 2002. Accepted 18 September 2002.

DOI: 10.1097/01.TP.0000041784.27763.A9