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Recent Advances in Hepatic Transplantation at the University of Pittsburgh

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We recently achieved 4 major advances in clinical hepatic transplantation at our center: first, the introduction and demonstration of the superior therapeutic index of the new immunosuppressive drug FK 506; second, the feasibility (with the aid of this drug) of combined liver-intestinal and multivisceral transplantation for patients with hepatointestinal failure; third, 2 attempts at hepatic xenotransplantation; and fourth, beginning attempts to induce donor-specific nonreactivity with adjuvant bone marrow more rapidly. These studies will be addressed separately because of the unique design of each and the heterogeneity of the enrolled patient population. The survival curves for both patients and grafts were estimated by the Kaplan-Meier (product-limit) method and the comparison among the different cohorts within each population was done by the generalized Wilcoxon (Breslow) test.

Clinical Evolution of FK506: 4 Years Experience

Since its discovery in 1983 and before its initial clinical use in February of 1989, the novel immunosuppressive drug FK506 underwent extensive in-vitro and animal studies (1,2). It was first used to salvage liver allografts that were failing because of rejection despite state-of-the-art treatment with conventional immunosuppression (3). The encouraging results of the rescue trial (4) justified the evaluation of FK506 as the primary immunosuppressant for our liver allograft recipients (5). Rather than summarizing our overall clinical experience with hepatic transplantation, we will focus on the therapeutic efficacy of FK506 among primary liver allograft recipients. The biocharacteristics, pharmacokinetics, and methods of assay of FK506 are fully described elsewhere (6-10).

Materials and Methods

Patient Population—From August 18, 1989 through August 1, 1993, 1,153 consecutive patients underwent primary liver transplantation and received FK506 as the primary immunosuppressive agent. The patient characteristics are summarized in Table 1. Of the 1,153 recipients, 84% were adults and 16% were children. The mean age was 51 ± 12 years (range: 18-76) for adults and 6±6 years (range:0.2-17.8) for children. Of the adult patients 251 (26%) were over 60 years of age. The indications for liver transplantation based upon the histopathologic diagnosis of the native liver disease are given in Table 2. Parenchymal liver diseases accounted for more than 50% of the cases. The urgency for transplantation for the majority of the patients was high, as defined by the United Network for Organ Sharing (UNOS) criteria that existed at the time (Table 1): a) working; b) home (many still working but requiring close medical supervision and/or sporadic hospital care.; c) hospital-bound continuously or the majority of the time; d) ICU-bound; and e) UNOStat, meaning a life

expectancy of only a few days without transplantation (11). Retransplantation was required for 138 (12%) patients; 122 had a second transplant, 15 had a third transplant and one had 3 additional grafts. All of the survival analyses were based on follow-ups until October, 1993.

Of the 1,153 FK506-treated patients, 612 were transplanted between February 19, 1990 and December 21, 1991. Seventy-nine of these 612 patients were part of the randomized trial that was conducted during that period comparing cyclosporine A (CsA) to FK506. The remaining 533 patients were excluded from randomization. The criteria of exclusion were; age less than 18 or more than 60 years, positive hepatitis B sAg, malignancy, multiple organ transplantation, renal failure, active infection, coma, significant heart or lung disease, previous hepatobiliary and/or portal hypertensive surgery, unsatisfactory recipient operation and liver allograft of uncertain quality (12). The differences between the randomized and nonrandomized patients are summarized in Table 3.

Immunosuppression—From the outset, FK506 was used for all patients. The early phase of the study was carried out during the learning curve in which the daily induction doses were 2 or 3 times greater than those currently recommended (8,13-15). Our present policy is to give FK506 initially intravenously as a continuous infusion at a dose of 0.05 mg/kg/day. The conversion from intravenous to oral therapy is usually made without any overlap with a starting oral dose of 0.1-0.15 mg/kg every 12 hours. Dose adjustments during both the intravenous or the oral administration of the drug were dictated by FK506 plasma trough levels, documentation of rejection, presence of adverse drug reactions with special emphasis of nephrotoxicity and neurotoxicity, evidence of infection, and functional status of the graft (13).

Immediately after graft reperfusion, one gram of methylprednisolone was administered intravenously. A daily dose of 20 mg of prednisone was started and reduced in 2 or 4 weeks in the absence of rejection. Thereafter, prednisone was weaned and frequently discontinued. The first 63 patients and those who had a strong positive cytotoxic crossmatch were given a 5-day steroid taper beginning at 200 mg/day for the first postoperative day with reduction of 40 mg/day until 20 mg/day was reached on the sixth day. Steroid doses were scaled down for children. Prostaglandin E_1 (prostin^R) was added to the immunosuppressive cocktail of some patients during the first postoperative week (16). A low dose of azathioprine (0.5-2 mg/kg/day) was given to about 10% of the patients at some time during the postoperative period.

When rejection occurred, it was treated with an increased maintenance dose of FK506 and a one gram bolus of either methylprednisolone or hydrocortisone. A steroid recycle and/or a 5-day course of OKT_3 (5-10 mg/day) was given to patients with moderate to severe rejection episodes.

Results

Total Population—Of the 1,153 liver recipients, 233 (20%) patients have died for reasons summarized in Table 4. With a mean (± SD) follow-up of 22±15 months (range: 3-49), the overall patient actuarial survival rates were 90%, 87%, 83%, and 75%, at 3, 6, 12 and 48 months, respectively (Fig. 1). With a total of 1,308 liver allografts, 155 (13%) failed. Rejection was the cause of failure of only 6 grafts (4%). The overall graft survival was 81%, 78%, 74%, and 65% at 3,6,12, and 48 months respectively (Fig. 1). The difference between patient and graft survival emphasizes the survival benefit of retransplantation.

Randomized versus Nonrandomized Groups—As expected, the highly selected randomized group (n=79) had significantly better patient (p=0.006) and graft (p=0.001) survival compared with the nonrandomized patients (n=533) who were excluded from the

randomized study (Fig. 2). The 2-year patient survival was 91% versus 76% with a graft survival rate of 88% versus 67%. The survival difference between the 2 groups reflects the cumulative detrimental effect of the exclusion criteria that were used for randomization.

Age Groups—Figure 3 illustrates the differences in patient survival among different age groups. Early survival rates for adults compared favorably with those for children. With long-term follow-up, however, the pediatric patients had a significantly ($p=0.02$) better survival compared with the adults (Fig. 3A). The senior group (>60 yrs of age), had a relatively higher risk score and experienced lower long-term survival compared with the younger adults (≤60 yrs) with a 2-year survival rate of 66% and 82%, respectively (Fig. 3B).

Medical Urgency—Using the 5-tier UNOS score, we were able to demonstrate the significant ($p<0.0001$) effect of disease gravity on the survival outcome after transplantation. The actuarial survival rate at 3, 12, and 24 months for patients called in to the hospital (UNOS 1 and 2) to receive a transplant was 93%, 87%, and 83%, respectively (Fig. 4). It was significantly ($p=0.0003$) less in UNOS 4 and 5 groups. However, between the first and second years following transplantation, the percentage of patient losses was lowest (3%) in the originally highest risk UNOS 4 and 5 groups.

Primary Liver Disease—Patients with either parenchymal or cholestatic liver disease had similar and high long-term survival rates with FK506-based immunosuppression (Fig. 5). The recent achievement of a high posttransplant survival rate (82% at 12 months) for patients with fulminant hepatic failure is attributed to the current monitoring of intracerebral blood flow and prevention of excess intracranial pressure in addition to the therapeutic advantage of FK506. As expected, recipients with a perioperative diagnosis of primary hepatic malignancy had the lowest long-term survival; 72% at one year and 59% at 2 years. The common cause of patients' death was tumor recurrence despite the utilization of pretransplant intra-arterial chemotherapy in some of these patients with or without posttransplant systemic chemotherapy.

Recurrence of Viral B Hepatitis—In a series of 78 consecutive patients with hepatitis B viral (HBV)-related diseases, 56% had disease recurrence with a median follow-up of 24 months. Those who have higher levels of HBV replications (n=8) as assessed by the presence of HBe antigen positivity, experienced a higher rate of disease recurrence (88%), and half of them (n=4) died of recurrent hepatitis. The use of hepatitis B immune globulin did not prevent disease recurrence but may have delayed its clinical onset.

Retransplantation—The need for graft replacement was significantly reduced with the use of FK506 (12%). Patient survival after retransplantation was 75% at 3 months and 54% at 2 years (Fig. 6).

Rejection—The incidence and treatment of liver allograft rejection under FK506 has been reported elsewhere (17). In summary, greater than 50% of the liver recipients were rejection free and nearly half of them were steroid free by 3 months after transplantation. Our initial experience with drug toxicity and development of opportunistic infections was documented previously (18,19) and has been updated recently (20-24). Drug interactions and other clinical observations were also published elsewhere (25,26).

The demonstration of the therapeutic efficacy of FK506 for clinical hepatic (12) and experimental visceral transplantation (27,28) revitalized our combined liver-intestinal and multivisceral transplantation program (29).

Hepatic-Intestinal Transplantation

Materials and Methods

Here we report our experience with the first 27 consecutive patients who were given liver allografts in continuity with the donor intestine (n=21) or as part of a multivisceral composite of abdominal splanchnic organs (n=6). The 27 patients (11 adults, 16 children) were treated between July 24, 1990 and April 15, 1993. All of the 21 patients who received liver plus intestine were jaundiced and had advanced hepatic disease with a mean (±SD) serum bilirubin of 19±14 mg/dl before transplantation. The causes of intestinal failure and indications for the 2 different operations are given in Table 5.

The multivisceral allografts included all of the usual multivisceral constituents; liver, pancreas, stomach, duodenum, and intestine. They were required in 5 adults and one pediatric patient. In 2 of the 5 adult cases, deficiency of protein S and antithrombin III underlay previous thrombosis of both the superior mesenteric artery and celiac axis. Because the liver is the source of these factors, its inclusion in the graft was mandatory even though hepatic failure was not present. Replacement of the native liver, stomach, pancreas, and intestine was mandatory in the third adult patient who had a neuroendocrine tumor with hepatic and mesenteric lymph node metastases. Multivisceral replacement was also necessary in the fourth case that had Budd Chiari syndrome with portal vein and abdominal cava thrombosis secondary to polycythemia vera. The fifth adult recipient had total enterectomy, celiac artery stenosis (90%), multistrictured common bile duct, and ligated main pancreatic duct. In the multivisceral pediatric recipient, the primary gastrointestinal disease (pseudo-obstruction) was involving the stomach and duodenum, and the liver failed because of TPN-induced cholestasis.

All of the cadaveric donors were ABO blood group identical with the recipients. HLA matching was random and uniformly poor. The lymphocytotoxic crossmatch was positive in 2 combined liver-intestinal recipients. No attempts were made to alter the graft immunologic tissue with irradiation, antilymphocyte preparations, or other modalities. The details of both the donor and recipient operations have been described elsewhere (30).

The management strategy for these unique liver recipients is described comprehensively in our recent publications (31,32). The basic immunosuppressive drug therapy was FK506 in addition to steroids and prostaglandin E_1. Augmented immunosuppression was initiated during rejection episodes, based upon severity. A steroid bolus was given and FK506 dosage was increased when this was possible without nephrotoxicity. A steroid recycle for 5 days and/or a 7-day course of OKT_3 were backup options.

Results

Patient Survival—During potential follow-ups of 6-39 months and as of October 1993, 9 (33%) of the 27 patients died: 8/21 combined liver and intestine, and 1/6 multivisceral. The causes of the 9 deaths were either technical complications (n=3), opportunistic infections (n=2), uncontrolled graft rejection (n=2), or disseminated posttransplant lymphoproliferative disease (PTLD) (n=2).

Six of the 8 mortalities after combined liver and intestinal transplantation were of children. Enteric and/or biliary leaks were responsible for 3 deaths. The other 3 were caused by respiratory syncytial viral pneumonia, refractory acute rejection, or PTLD (one example each). One of the 2 liver-intestine adult recipients died of hepatorenal failure combined with chronic rejection and the other succumbed to disseminated coccidiomycosis. The only death in the multivisceral series was caused by PTLD which was diagnosed at autopsy 49 days posttransplantation.

The actuarial survival rate for the 27 patients at 3, 6, 12, and 24 months was 82%, 79%, 74%, and 69%, respectively (Fig. 7). The mean follow-up period was 16±12 months for liver plus intestine and 11±8 months for multivisceral recipients. At 3 months, the survival rate for the combined liver-intestine recipients was 81% and 86% for the multivisceral recipients. At one year following transplantation, these estimates were 71% and 86%, respectively. At 2 years, the actuarial survival rate was 65% for the combined liver intestinal recipients and 86% for those who received multivisceral grafts.

Graft Survival—The estimated actuarial survival for all of the grafts (n=28) was 76%, 76%, 71%, and 67% at 3, 6, 12, and 24 months, respectively (Fig. 8). Graft survival was higher during the entire follow-up period for the multivisceral cases compared to those with combined liver-intestine. All but one graft was lost due to patient's death. The only graft removed at reoperation was a liver-intestine transplanted to a child across a strong positive cytotoxic crossmatch. Although graft removal and retransplantation after 47 days was technically successful, refractory rejection of the second set of organs caused death after another 60 days. Loss of part of these composite grafts occurred in 2 recipients because of either severe preservation injury of the pancreas necessitating pancreatectomy, or hepatic artery thrombosis necessitating replacement of the liver graft.

Rejection—Whereas 16 patients did not experience rejection of the liver allograft, only 2 (both with combined liver-intestine) were spared clinical or histopathological diagnosis of intestinal allograft rejection. Consequently, the incidence of intestinal allograft rejection (93%) was higher than that of the liver allografts (43%). Also, the episodes of rejection per graft were higher for the intestine (4.1) compared with the liver (0.6). The mean postoperative time to the first episode was 22±34 days for the combined liver and intestine, and 15±7 days for the multivisceral allografts. Liver and small bowel biopsies were taken simultaneously or closely together on 88 occasions; 47 (53%) of the dual specimens had no signs of rejection in either organ, 12 (14%) had rejection in both, 15 (17%) had rejection only in the liver, and 14 (16%) had rejection in the intestine only. Chronic rejection was the cause of graft failure in one adult recipient with combined liver-intestine who had a strong positive cytotoxic crossmatch.

Graft-versus-Host Disease (GvHD)—Using standard histology and in situ hybridization techniques that allow distinction of donor from recipient cells, GVHD was unequivocally diagnosed in only one combined liver-intestinal pediatric recipient. Light immunosuppression was attempted early in the postoperative course of this child because of Pneumocystis carinii pneumonia and an intestinal anastomotic leak. The skin lesions appeared 10 days after transplantation and the overall clinical picture simulated life-threatening sepsis. The immunosuppression was reduced significantly and 13 days later, the patient succumbed to multiple organ failure.

Postoperative Course—The early convalescence of most of the recipients was prolonged and complicated because of recurrent rejection and/or infection (32). Nonetheless, 16 (89%) of the 18 current survivors are home, free of TPN, and enjoying unrestricted oral diets.

Clinical Xenotransplantation

Materials and Methods

In June 1992 and January 1993, 2 male patients aged 35 and 62 years, with end-stage liver disease due to chronic B viral active hepatitis had their cirrhotic livers replaced with baboon livers (33,34). These efforts were prompted by the worldwide shortage of donor organs and

by evidence that baboon livers would be resistant to the hepatitis B virus that reinfects most hepatic allografts. Extensive infectious surveillance was performed for both donors. Both recipients had ABO-compatible grafts. The conventional lymphocytotoxic crossmatch of both recipient sera to their donor lymphocytes was positive in both cases but negative after dithiothreitol treatment. A full description of both donors and recipients has been published elsewhere (33,34).

The surgical techniques were adapted from hepatic allotransplantation (35). Although the baboon donors were large, their body weights were only 40% of the recipients, necessitating the so-called piggyback operation which leaves the recipient vena cava intact. The surgical procedure in both cases was satisfactory initially and during the postoperative course, there was radiologic and histopathologic evidence of liver regeneration and increased graft volume (33,34).

The immunosuppressive cocktail used for prevention and control of rejection of the 2 hepatic xenografts was made by FK506, steroids, cyclophosphamide, and prostaglandin E_1. Doses and routes of administration are shown in Figures 9 and 10. Detailed descriptions of the immunosuppressive therapy and drug blood levels were recently reported elsewhere (34).

Results

The first recipient awoke promptly from anesthesia, resumed diet and ambulation, and was jaundice-free for most of the 70 days of survival. However, the canalicular enzymes were high from the second week onward (Fig. 9). Two months after transplantation, icterus finally developed and it was ascribed to partial obstruction of the reconstructed bile duct. At autopsy, the entire biliary tract was filled with inspissated bile, and most of the biliary ducts were denuded of epithelium. In contrast, the second patient remained icteric (Fig. 10) and comatose after the operation. The xenograft had the same cholestatic picture as the first one despite adequate biliary anastomosis. In both patients, the jaundice was not particularly responsive to augmented immunosuppression with steroid boluses and increased maintenance doses of prednisone. Hypoalbuminemia was evident in both patients (<2 gm%) in spite of other adequate synthetic function including prothrombin time (34). Renal failure was inevitable in both patients. It developed in the first recipient after 21 days, whereas the second patient became anuric immediately after the transplantation.

Although the cause of death in both cases was multifactorial, the first recipient succumbed to ruptured intracerebral mycotic aneurysm due to disseminated aspergillosis and the second died of peritonitis secondary to an anastomotic leak at the jejunojejunostomy of the Roux-y biliary reconstruction (34). Meanwhile, neither of the 2 hepatic xenografts provided adequate function despite the absence of significant histopathologic abnormalities. Immunoperoxidase staining revealed no evidence of reinfection of the hepatic allograft with HBV in either case.

There was little histopathologic evidence of humoral or cellular rejection of these 2 liver xenografts. Only one of the 5 biopsies obtained from the first patient (postoperative day 12) had a mild focal cellular rejection and none of the 7 biopsy samples taken from the second patient showed any definite evidence of cellular rejection by the conventional criteria used for hepatic allografts. The hepatic xenograft of both patients was entirely free of any histopathologic evidence of arteritis during the entire postoperative course. However, sludging as well as the presence of polymorphonuclear leukocytes was seen in the sinusoids of the xenografts immediately after reperfusion, compatible with the diagnosis of an aborted hyperacute rejection (36). During the first 2 weeks after transplantation, the total complement was depleted while complements C_3, C_4, and C_5 became undetectable. During

this time, there was binding of IgM and IgG in the grafts with appearance of circulating immune complexes (36). After 10 days, the complement system settled down but irreversible damage may have been done which could be reflected in the form of diffuse fine microsteatosis of the graft.

Induction of Graft Acceptance

It is not understood how allografts are able to weather the initial attack by the recipient immune system and later to provide increasingly stable function with less and less need for therapy. Study of the gastrointestinal organs and their recipients have provided unique insights into these processes (37-41). In 1969, it was noted that the Kupffer cells and other tissue leukocytes became predominantly recipient phenotype within 100 days after transplantation while the hepatocytes retained their donor specificity permanently. For a long time, this transformation was assumed to be unique to the hepatic allograft.

However, 22 years later, first in rat models, and then in humans, it was realized that the same process occurred in all successfully transplanted intestines and other organs, differing only quantitatively in the number of substituted tissue leukocytes which was greatest with the liver. In 1992, the fate of the leukocytes vacating the grafts was learned by studying the longest survivors in the world after kidney (30 years) or liver transplantation (23 years). Biopsies were obtained from these patients and also from more recently treated recipients of hearts, lungs, and intestines. Samples were taken from the transplanted organ as well as from the patient's own skin, lymph nodes, and other tissues.

After special staining procedures (immunostaining or sex identification after fluorescence in situ hybridization [FISH]), it was possible to determine if the individual cells had come from the organ donor, the recipient's own body, or both. In confirmatory investigations, the donor and recipient contributions to any specimen could be separated by polymerase chain reaction (“DNA fingerprinting”) techniques.

From these analyses and from supporting laboratory experiments in animals it was clear that within minutes after restoring the blood supply of any transplant, myriads of sessile, but potentially migratory leukocytes that are part of the normal structure of all organs (passenger leukocytes), left the graft and migrated ubiquitously, while being replaced in the transplant by similar recipient immunocytes under the cover of immunosuppressive drugs (Fig. 11). In this new context, the drugs could be viewed as traffic directors, allowing movement of the white cells to and from the graft but preventing the immune destruction that is the normal purpose of this traffic.

It is not known yet how the 2 sets of white cells - a small population from the donated organ and a large one that is, in essence, the entire recipient immune system of the patient - reach an immunologic “truce.” However, this is so complete in some cases that immunosuppression can be stopped, particularly after liver transplantation but less constantly with other organs. Such a stable biologic state can be induced more easily by the liver than by other transplanted organs because of the liver's higher content of the critical leukocytes that apparently included pluri-potent stem cells.

We have postulated that the previously unrecognized migration from organ allografts of donor leukocytes and their ubiquitous persistence in recipient tissues is the seminal explanation for allograft acceptance and the first stage in the development of donor specific nonreactivity (tolerance) (37-41). With this hypothesis, we undertook the augmentation of the donor leukocyte load with a perioperative infusion of nondepleted bone marrow in 16 nonconditioned recipients of livers (n=6), kidneys (n=9), and a heart including 3 diabetics who also were given pancreatic islets. All 16 have good organ transplant function and easily

detectable blood macrochimerism (1-15%) after one to 12 postoperative months. None have had significant GvHD. It is too early to attempt discontinuation therapy, but serial in-vitro testing has revealed a pronounced trend to donor-specific nonreactivity (tolerance).

Discussion

During the last decade, survival after liver transplantation has improved significantly with advanced medical technology, greater surgical experience, better organ preservation, and new, more effective immunosuppressive agents. The recent introduction of FK506 has further improved the survival and quality-of-life advantage of hepatic transplantation when compared with our previous experience (42). A summary of the worldwide experience with FK506 was presented during the 1991 First International Congress on FK506 and has been published elsewhere (43); the drug recently completed its “fast track” journey through the FDA.

With the evolution of a potent immunosuppressive drug like FK506, further improvement in patient and graft survival may only be possible by perfecting the surgical techniques with early detection and prompt correction of technically flawed operations (44). However, even with a perfect operation, recurrence of the primary liver disease is a major threat to graft and patient survival after liver transplantation. It is well known that candidates with either active viral hepatitis and/or liver malignancy remain at high risk of disease recurrence. The results of our cumulative experience with the prophylactic or therapeutic use of antiviral agents have been unsatisfactory (45-47). A role may emerge for thymosin, the new immunomodulator for prevention or treatment of recurrent viral hepatitis among liver allograft recipients. The survival benefit of our current protocol of treating liver recipients carrying the perioperative diagnosis of primary liver malignancy with intra-arterial and/or systemic chemotherapy have yet to be determined, but the early results are less encouraging than hoped for.

The survival outcome after liver transplantation is profoundly influenced by the recipient's condition at the time of surgery, particularly if the preterminal or terminal stages (UNOS 4 and 5) are reached. The best postoperative 2-year survival rate was in the lowest risk UNOS 1, 2, and 3 patients (83% combined) and the worst results were those in UNOS 4 and 5 (76% combined). The continuing shortage of organs for transplantation compounded by the current organ allocation policies in the United States continues to impose a significant mortality among the high-risk categories while awaiting for liver replacement (48).

The recent achievement of satisfactory long-term survival of patients treated with combined liver-intestinal and multivisceral transplantation is justification for continuation of trials. However, the surveillance and intensity of care required for these patients for the first year and in most instances thereafter was very high, far more than at comparable times after transplantation of the liver alone. Further immunologic and surgical strategies, however, are required to increase the practicality and success of such creative surgery (32).

Although our 2 recent attempts at baboon-to-human xenotransplantation failed, there were encouraging notations. First, the xenografts had no evidence of B virus infection during their posttransplant survival of 70 and 26 days in B virus carriers. Second, there also was little histopathologic evidence of humoral or cellular rejection of both liver xenografts. Nonetheless, the function of both xenografts was unsatisfactory. This could be explained by a damage caused by a complement activation syndrome precipitated by classical pathway or independent of antibodies (alternative pathway). It also has not been determined if interspecies metabolic differences will be significant long-term problems (36).

The discovery of chimerism in allograft recipients has important scientific and therapeutic implications. Because the chimeric leukocytes dispersed from the allograft are of bone marrow origin, a therapeutic corollary was that acceptance of less favored organs such as the heart and kidney (or even the liver itself) could be facilitated by the infusion of unaltered donor bone marrow perioperatively. Donor leukocyte infusion to induce tolerance was the most therapeutic strategy of transplantation immunology but perhaps the least well understood. It was first used by Prehn and Main (49) who showed that lethally irradiated adult mice reconstituted with allogeneic bone marrow could accept skin from the same donor strain but no other. These were efforts to mimic the 2 conditions (inoculation of mature donor immunocytes and immunologic nonreactivity of recipients) that had allowed Billingham, Brent, and Medawar (50) to induce acquired tolerance of neonatally or perinatally injected mice. Thousands of similar experiments, as well as the treatment policy in the clinical field of bone marrow transplantation, have assumed the need either for a natural or imposed state of host nonreactivity. The consequent risk of GvHD from liver donor cells described by Billingham and Brent (51) has been so great with MHC incompatibility that for the most part, their use has been avoided only if they were killed.

Armed with the discoveries that natural chimerism from the graft itself begins within minutes of organ revascularization and persists, during 1993 it was possible to simulate this timing in unconditioned patients whose transplanted organ, routine immunosuppression, and adjuvant bone marrow all arrived perioperatively. The benign course of all recipients had 0.8% to 15% circulating donor leukocytes from one to 12 months later was consistent with the earlier observation in rodents by Slavin and Strober (52) and Ildstad and Sachs of GvHD resistance of mixed chimerism (53).

Summary

FK506 undoubtedly improved the survival advantage of hepatic allotransplantation. Hepatic-intestinal and multivisceral transplantation has also become a feasible therapy for patients with combined intestinal and liver failure. With better understanding of the immunologic and metabolic aspects of allo- and xenotransplantation, further clinical attempts to transplant animal organs to humans may be considered with the hope for a better outcome in the very near future.

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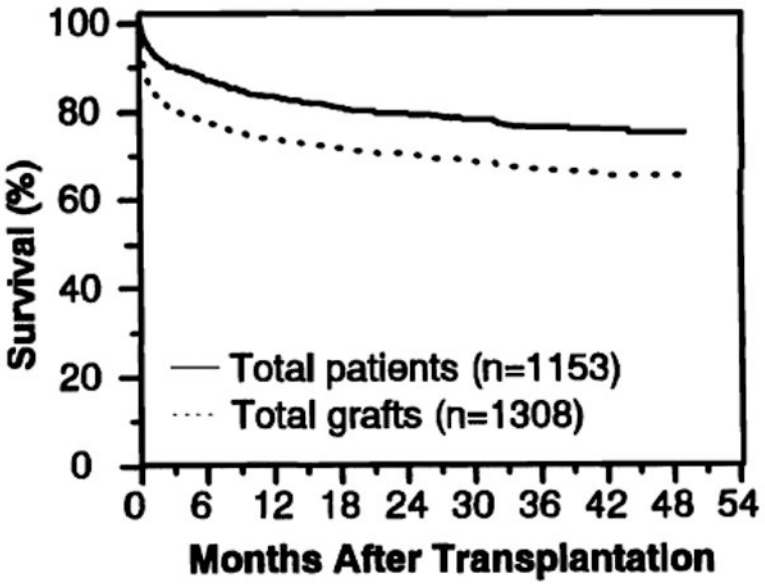

Figure 1.
The Kaplan-Meier (actuarial) patient and graft survival for primary liver allograft recipients who received FK506 as the primary immunosuppressive drug therapy.

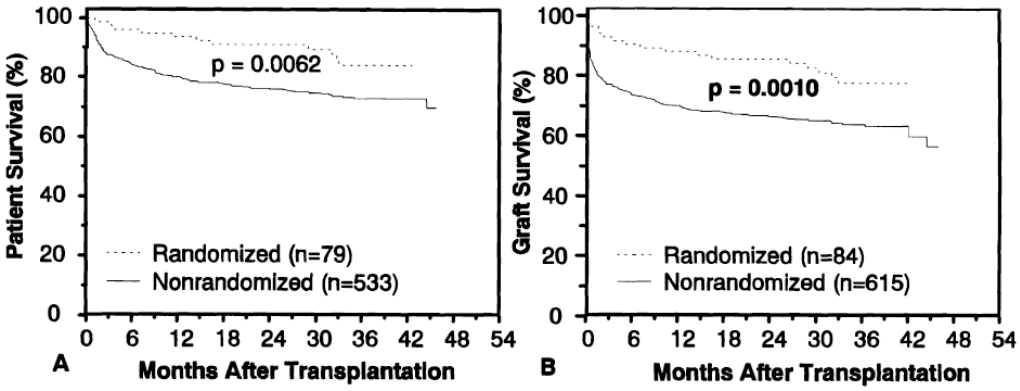

Figure 2.

The actuarial patient (A) and graft (B) survival for primary liver recipients that were transplanted during the period of the randomized study (Feb. 1990-Dec. 1991).

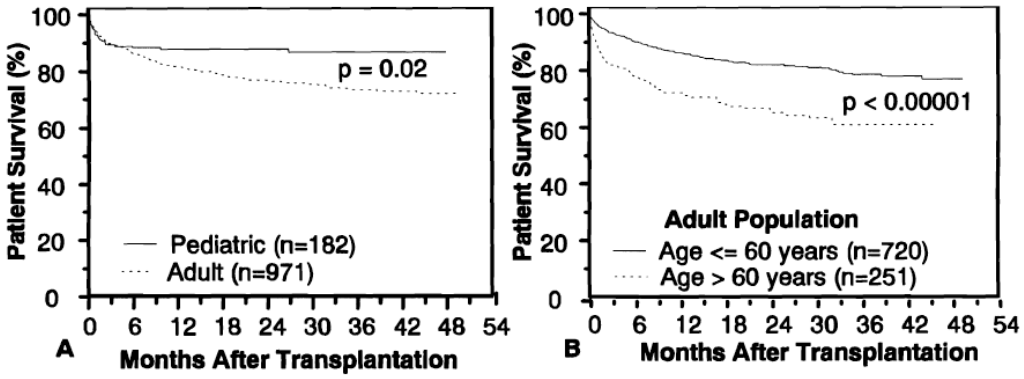

Figure 3.

The estimated (Kaplan-Meier) survival for liver recipients according to their age. A) pediatrics versus adults; B) patients over age 60 versus younger adult recipients.

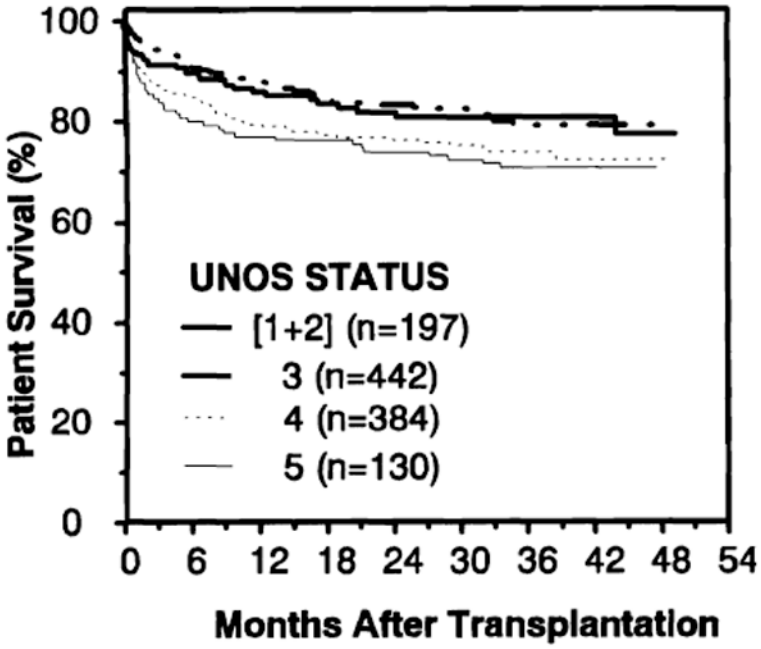

Figure 4.
Patient survival after liver transplantation stratified according to the medical urgency for surgery as defined by the standard criteria of the United Network for Organ Sharing (UNOS).

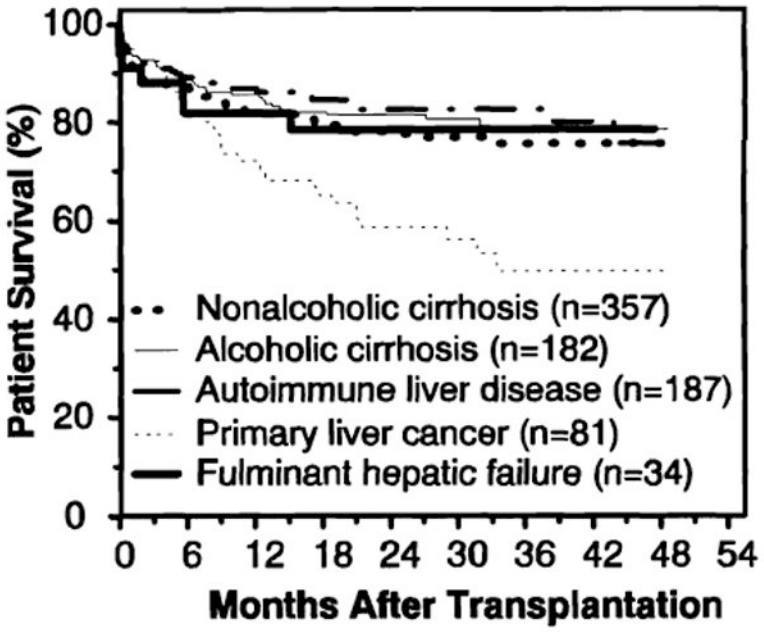

Figure 5.
Survival of FK506 primary liver allograft recipients stratified according to the pathology of the primary liver disease.

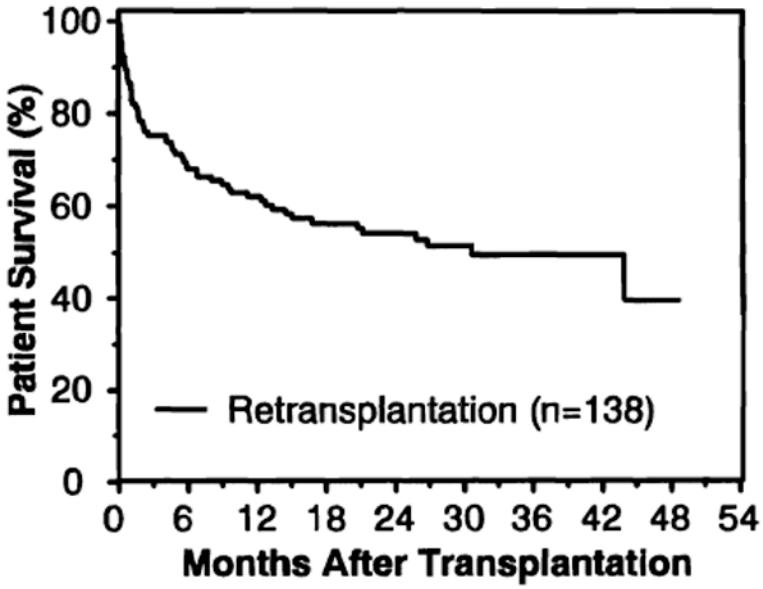

Figure 6.
The actuarial patient survival after retransplantation.

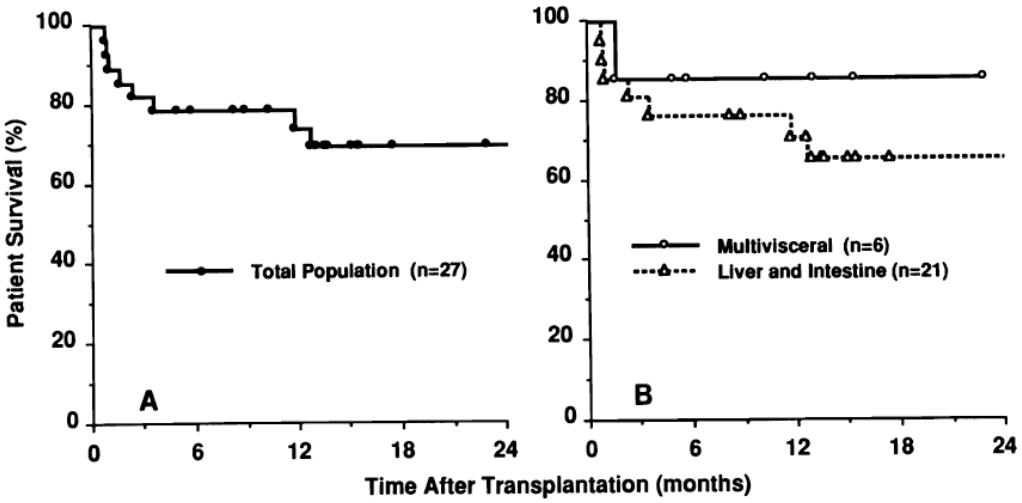

Figure 7.
Survival of the combined liver-intestinal and multivisceral recipients. A) all 27 patients; B) according to procedure.

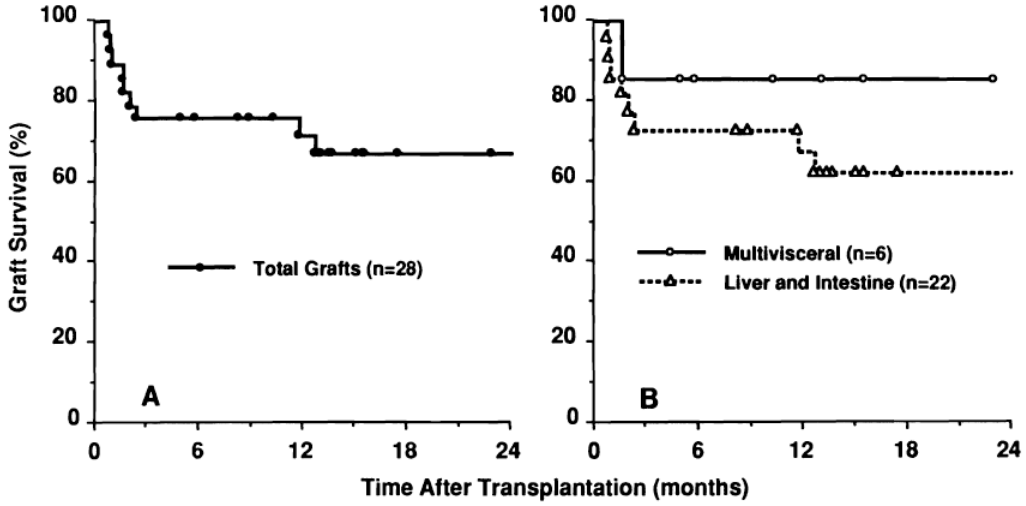

Figure 8.
Survival of the combined hepatic-intestinal and multivisceral grafts. A) all 28 attempts including one retransplantation; B) according to procedure.

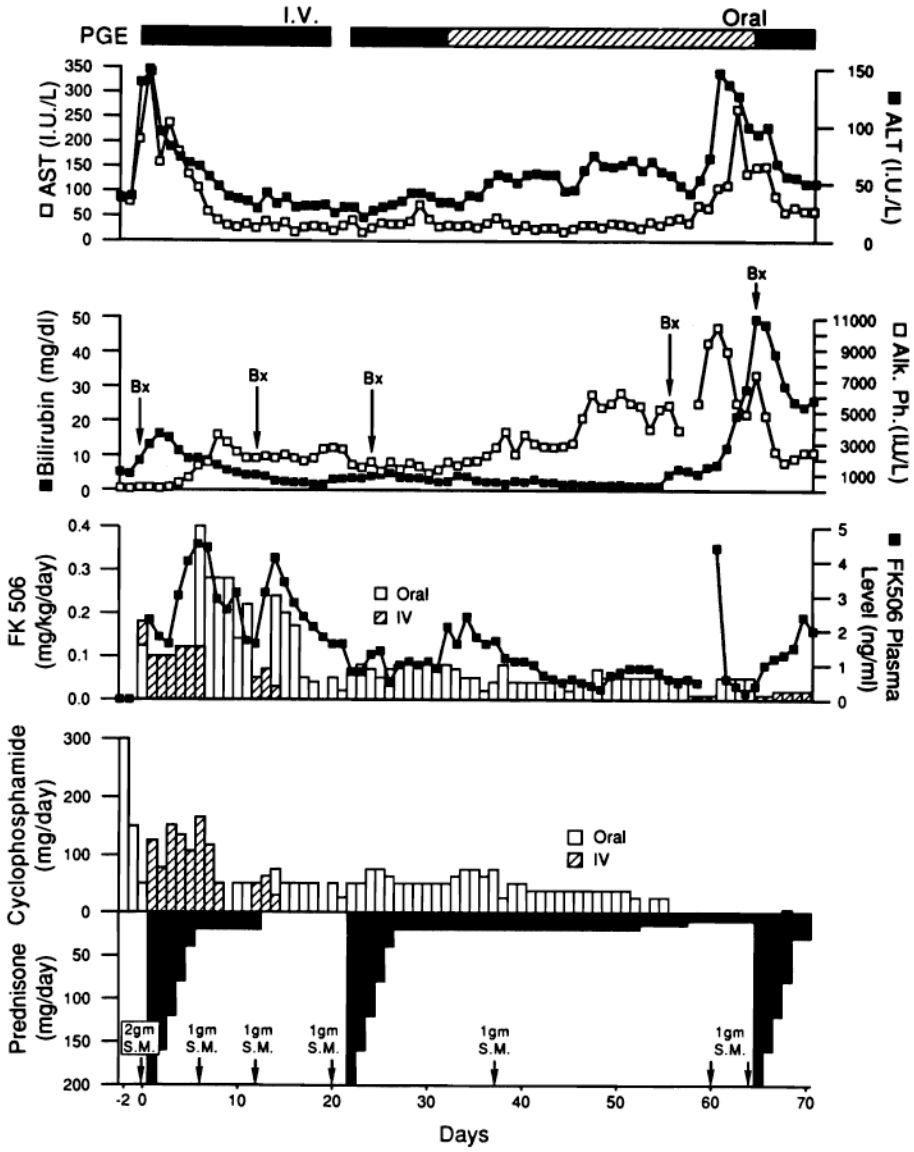

Figure 9.

Clinical course of the first liver xenograft (baboon-to-human) recipient.

SM, Solumedrol (methylprednisolone); PGE, prostaglandin E; Bx, biopsy; ALT, alanine aminotransferase; Alk Ph, alkaline phosphatase. (From: Starzl TE, Fung J, Tzakis A, Todo S, Demetris AJ, Marino IR, Doyle H, Zeevi A, Warty V, Michaels M, Kusne S, Rudert WA, Trucco M: Baboon-to-human liver transplantation, Lancet 1993; 341:65-71, Used by permission).

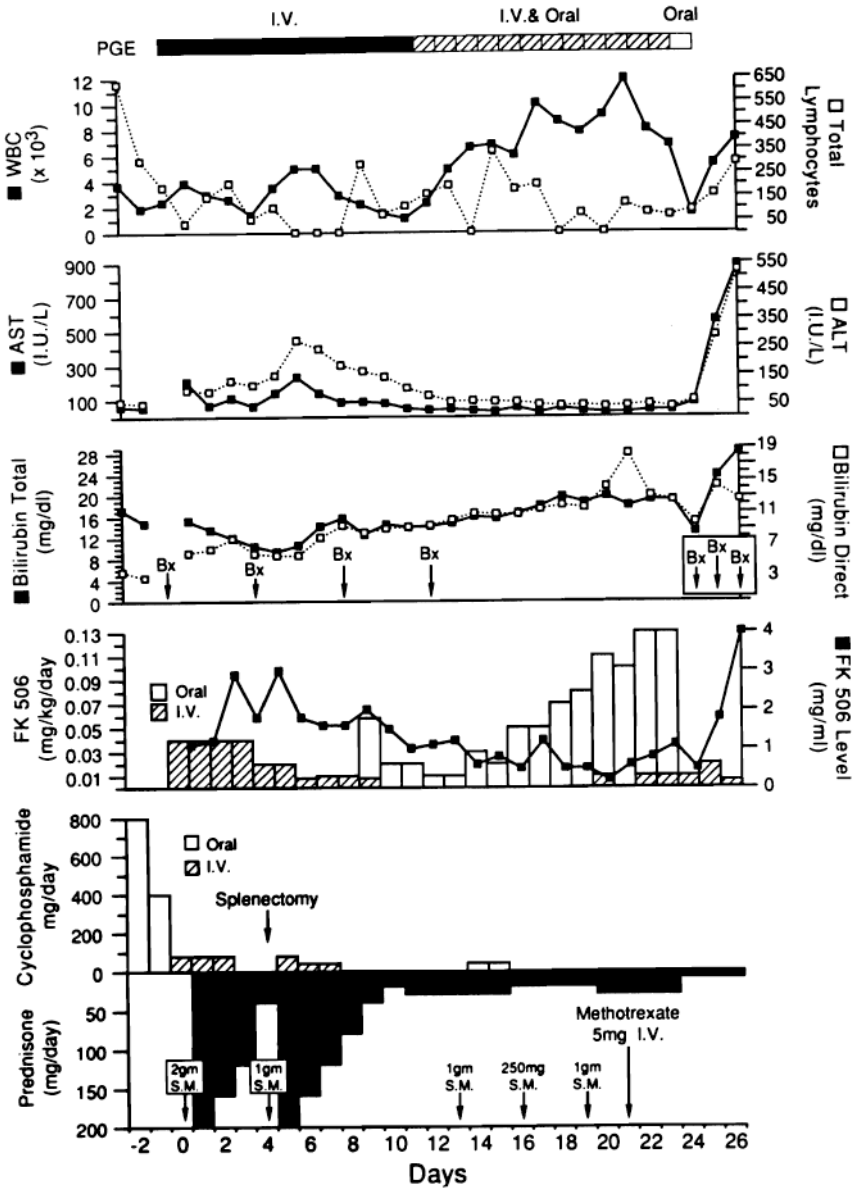

Figure 10.

Clinical course of the second liver xenograft (baboon-to-human) recipient.

SM, Solumedrol (methylprednisolone); PGE, prostaglandin E; Bx, biopsy; ALT, alanine aminotransferase; WBC, white blood cells, (From: Starzl TE, Tzakis A, Fung J, Todo S, Marino IR, Demetris AJ: Human liver xenotransplantation. Xeno 1993; 1(1):4-7. Used by permission).

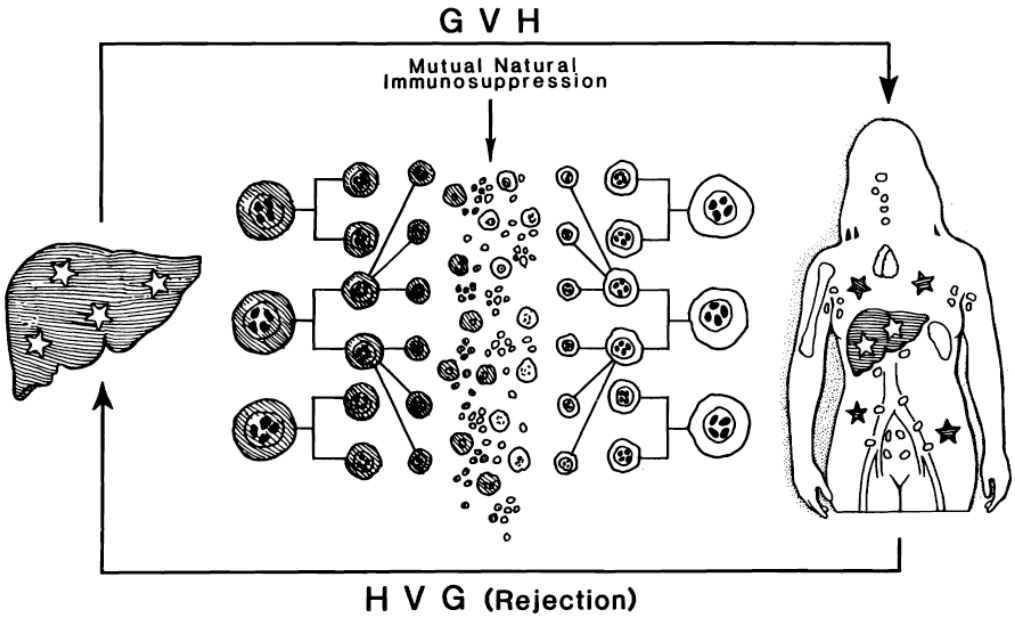

Figure 11.
The mutual engagement of migratory immunocytes from the graft and the recipient following organ transplantation under potent pharmacological immunosuppression. GVH: graft versus host; HVG: host versus graft. (From Starzl TE, Demetris AJ, Murase N, et al. Donor cell chimerism by immunosuppressive drugs: a new view of organ transplantation. Immunol Today 1993; 14:326. Used by permission)

Table 1

Characteristics of the patient population and the severity of the clinical condition before the liver transplant.

	n	(%)
Patient Populations		
Number of patients	1,153	
Adult	971	
Pediatric	182	
OLTx II	122	
OLTx III	15	
OLTx IV	1	
Number of grafts	1,308	
Age total		
(mean ± SD, Year)	43±21	
Adult	51±12	
Pediatric	6±6	
Sex (M/F)	695/458	
UNOS Score		
1	7	(0.6)
2	190	(17.0)
3	442	(38.0)
4	384	(33.0)
5	130	(11.0)

OLTx = Orthotopic liver transplantation

UNOS = United Network for Organ Sharing

Table 2

Indications for primary liver transplantation under FK506 therapy.

	n	(%)
Nonalcoholic cirrhosis	384	(33)
Alcoholic cirrhosis	210	(18)
Autoimmune disorders	204	(18)
- autoimmune hepatitis	38	
- primary biliary cirrhosis	92	
- primary sclerosing cholangitis	74	
Biliary atresia	93	(8)
Genetic disorders	30	(3)
Primary liver cancer	81	(7)
Fulminant failure	34	(3)
Miscellaneous	117	(10)

Table 3

Clinical features of the randomized and nonrandomized patients who received primary liver transplantation between February 1990 and December 1991 under FK506.

	Nonrandomized (n=533) n (%)	Randomized (n=79) n (%)
Number of patients		
Adults	429	79
Children	104	0
OLTx II	70	5
OLTx III	6	0
Number of grafts	615	84
Liver disease		
Nonalcoholic cirrhosis	15 (28)	27 (34)
Alcoholic cirrhosis	92 (17)	28 (35)
Autoimmune disorders	78 (15)	17 (22)
Biliary atresia	59 (11)	2 (3)
Genetic disorders	14 (3)	1 (1)
Tumor	55 (10)	0 (0)
Fulminant failure	23 (4)	0 (0)
Others	61 (12)	4 (5)
UNOS score		
1 + 2	68 (13)	12 (15)
3	184 (35)	37 (47)
4	195 (36)	19 (24)
5	86 (16)	11 (14)

Table 4

Causes of death after primary liver transplantation under FK506 therapy.

	n	(%)
Fulminant infection	99	(9)
Graft failure	24	(2)
Malignancy	21	(2)
Cardiovascular	18	(1)
Others	46	(4)
Unknown	25	(2)
Total	233	(20)

Table 5

Causes of intestinal failure and indications for combined liver-intestinal and multivisceral transplantations.

Cause	Adults (n=11) Intestine + Liver	Multivisceral	Cause	Children (n=16) Intestine + Liver	Multivisceral
Crohn's disease	1	0	Gastroschisis	5	0
Abdominal trauma	2	0	Necro. enterocolitis	4	0
Celiac A occlusion	0	3*	Volvulus	3	0
SMA thrombosis	2	0	Intestinal atresia	2	0
Desmoid tumor	1	0	Microvillus disease	1	0
Metastatic gastrinoma	0	1	Pseudo-obstruction	0	1
Budd-Chiari syndrome	0	1			

* These patients had short-gut syndrome due to concomitant superior mesenteric artery (SMA) thrombosis by protein S deficiency (n=1), antithrombin III deficiency (n=1), or unknown cause (n=1).