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Auxiliary partial orthotopic liver transplantation for acute liver failure

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Background/Aims: **Auxiliary partial orthotopic liver transplantation holds potential advantages over conventional orthotopic liver transplantation, but experience with the technique in acute liver failure is limited.**
Methods: **We describe our initial experience in seven patients (4 men, 3 women; mean age 28, range 14–35 years) with acute liver failure (paracetamol 3, non A–E 2, autoimmune 1, Ecstasy 1) who fulfilled criteria for emergency transplantation. Preoperatively, the median international normalised ratio was seven (range 3.4–15), with a creatinine of 123 μM (51–389 μM) and bilirubin 320 μM (61–572 μM). The reasons for performing an auxiliary transplant were the patients' young age and stable preoperative condition (n=5), or a significant psychiatric history precluding conventional transplantation (n=2).**
Results: **All patients received blood group-matched left (n=2) or right (n=5) auxiliary grafts. Median duration of surgery was 8.5 h (7.3–10 h), with blood loss of 8.3 litres (4.6–14.6 litres). Post-transplant, the international normalised ratio and aspartate aminotransferase fell progressively in all patients, with median values at day 7 of 1.4 (1.0–2.4) and 108 IU/l (78–910 IU/l). Three patients died from sepsis within the first postoperative month. At 2 weeks, four of six patients had partial regeneration of the native liver, which became complete in two of the survivors by 1 year.**
Conclusions: **Although patient selection remains poorly defined, auxiliary partial orthotopic liver transplantation in acute liver failure is technically feasible and, in some patients, allows native liver regeneration and eventual immunosuppression withdrawal.**

Key words: **Acute liver failure; Auxiliary partial Orthotopic liver transplantation.**

ORTHOTOPIC liver transplantation (OLT) is an established treatment for acute liver failure, with 1-year patient survival rates of approximately 60–70% (1–3). At King's College Hospital, the decision to proceed to OLT is based on clinical and laboratory criteria which predict a survival rate without transplantation of less than 20% (4). Thus, OLT for acute liver failure (ALF) represents a considerable improvement on medical management alone in this group of patients. Nevertheless, a significant minority of patients with ALF who fulfil transplant criteria would have had complete morphologic and functional recovery of their liver if they had not undergone OLT (5,6).

These considerations have led to the concept of auxiliary liver transplantation, which does not exclude the potential for spontaneous regeneration of the native liver and eventual withdrawal of immunosuppressive drugs. In this technique, a healthy liver graft is placed either heterotopically or orthotopically while leaving all or part of the native liver *in situ* (7). However, early experience with heterotopic placement of the auxiliary graft in patients with ALF has been disappointing (7,8), partly because of inadequate portal perfusion of the graft and insufficient drainage of hepatic venous blood in an area of low pressure (9–12).

Recently, some centres have reported a favourable outcome following auxiliary partial orthotopic liver transplantation (APOLT) in children with inborn errors of metabolism (13,14). However, experience of this technique in patients with ALF is limited (15–18). In a workshop held in Strasbourg in 1994, the results of 23 orthotopic auxiliary transplants from 12 European centres were reviewed, and have been published

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recently (17). The details of eight of these patients has also been published as a single-centre series (18). In the 23 patients, a number of different surgical techniques, using left or right auxiliary grafts, were employed. After a median follow-up of 11 months, the overall survival rate was 69%, and immunosuppression was successfully stopped in two-thirds of the survivors.

The aim of the present study was to describe our initial experience with APOLT in ALF, with particular reference to: (i) the selection of patients, (ii) the use of a right or a left auxiliary graft, (iii) surgical complications and postoperative morbidity and mortality, and (iv) the frequency of native liver regeneration and immunosuppression withdrawal.

Methods

Patients

Between March 1994 and September 1995, seven patients (four men and three women) with a mean age of 28 (range, 14–35) years, underwent APOLT for ALF at King's College Hospital. In four patients, the cause of ALF was drug-related hepatotoxicity (paracetamol in three, "Ecstasy" in one), while two patients had presumed viral-induced (non A–E) ALF and one had fulminant autoimmune hepatitis (Table 1). All patients developed grade III–IV encephalopathy, and were intubated and ventilated electively. Intravenous N-acetylcysteine and antimicrobial prophylaxis were given according to our standard protocol (19). As part of a clinical trial (20), the first two patients were treated with an extracorporeal liver assist device (Hepatix Inc., Houston, Texas) (21) for 3–66 h before being listed for transplantation. At the time of transplantation, the median values for the International Normalised Ratio (INR), serum creatinine and bilirubin were 7.0 (range 3.4 to >15), 123 μmol/l (51–389 μmol/l) and 320 μmol/l (61–572 μmol/l), respectively (Table 1). At the time of transplantation, two of the seven patients required inotropic support, but none had clinical evidence of cerebral oedema.

Selection criteria for APOLT

At the time of being placed on the priority list for a donor liver, each patient fulfilled the King's College Hospital criteria for transplantation in ALF (4,22). By the classification of O'Grady et al. (23), three patients had hyperacute liver failure, while two each had acute or subacute liver failure, respectively. Of the three patients with paracetamol hepatotoxicity and hyperacute liver failure, all had a severe coagulopathy (INR 7.0 to >15) and renal failure (creatinine 277–389 μmol/l), and two had a marked metabolic acidosis (arterial pH <7.3). Of the four patients with non-paracetamol causes of ALF, all had INRs of >3.5, serum total bilirubin concentrations of >300 μmol/l, and jaundice to encephalopathy times of at least 7 days (Table 1).

In five patients, the reasons for performing a partial auxiliary liver transplant, rather than a conventional OLT, were their young age and stable condition preoperatively. In two patients, a significant psychiatric history and poor compliance with previous medications were considered to preclude OLT, but not an auxiliary graft.

Operation details

The first two patients underwent a left APOLT. After full mobilisation of the native liver, with ligation and division of the right adrenal vein, the left lateral segment (segments II and III) and the caudate lobe were excised. An infra-renal iliac conduit was anastomosed end-to-side to the aorta and taken through the transverse mesocolon and behind the stomach to the graft. The donor liver was cut down to a left lobe graft, retaining the common hepatic artery attached to a Carrel patch and the main portal vein. The inferior vena cava was side-clamped vertically and the donor

TABLE 1

Preoperative clinical details of the seven patients with acute liver failure

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age/sex	14/M	23/F	36/F	29/F	33/M	32/M	32/M
Cause of liver failure	Non A–E	Ecstasy[1]	Paracetamol	Paracetamol	Paracetamol	Non A–E	Autoimmune
Liver failure grading (ref. 23)	Subacute	Subacute	Hyperacute	Hyperacute	Hyperacute	Acute	Acute
Encephalopathy grade at listing	III	II–III	III	III	III	III	III
Arterial pH (normal 7.37–7.47)	7.35	7.40	7.34	7.15	7.06	7.37	7.30
Creatinine (normal <110 mol/l)	73	51	389	277	355	108	142
INR[2] (normal <1.2)	3.7	3.4	9	15	>15	4.4	7.9
Bilirubin (normal <13 mol/l)	555	320	92	61	57	572	559
Aspartate aminotransferase (normal <35 IU/l)	2450	370	3559	4822	13.000	2004	1031

[1] Ecstasy = 3,4-methylenedioxymethamphetamine (MDMA).
[2] INR = International Normalised Ratio.

suprahepatic vena cava anastomosed to the recipient suprahepatic vena cava at the level of the origin of the hepatic vein. Portal venous inflow was established by an end-to-side anastomosis. The common hepatic artery of the donor was anastomosed to the iliac conduit, and biliary drainage of the auxiliary graft established by a Roux-en-Y hepaticojejunostomy.

Based on the clinical course of the first two patients, it was considered that the necrotic right liver lobe retained in a left APOLT may have contributed to the development of a "toxic liver syndrome" post-transplant. Consequently, in the next five patients a right APOLT was performed. In this technique, the right lobe of the native liver was fully mobilised from the inferior vena cava. The right, middle and left hepatic veins were isolated, and an extended right hepatectomy performed. The donor liver was implanted following a left lateral segmentectomy, and the donor suprahepatic vena cava anastomosed to the origin of the right hepatic vein. The portal vein was then anastomosed end-to-side with the main trunk of the recipient portal vein, using a continuous Prolene suture and leaving a growth factor of one-third the portal vein diameter. Finally, the donor hepatic artery was anastomosed to an iliac conduit, and a Roux-en-Y hepaticojejunostomy performed.

Postoperative management

Postoperatively, the patients received a standard immunosuppression regime of tacrolimus in a dose of 5 mg twice daily by nasogastric tube (adjusted to maintain a trough whole blood level of 15–20 μg/l), and intravenous methylprednisolone (20 mg/day). Intravenous amphotericin (1 $mg \cdot kg^{-1} \cdot day^{-1}$) and broad-spectrum antibiotics were also prescribed (19).

Graft function was monitored by the daily measurement of the INR and liver function tests. Doppler ultrasonography of the liver was performed approximately twice weekly. In patients who survived the early postoperative period, ultrasound-guided, percutaneous, fine-needle biopsies of the donor and native lobes and, in selected patients, hepatobiliary scintigraphy with technetium-99m-labelled trimethyl-Br-imidodiacetic acid (IDA) (CIS bio international, France) were performed, at approximately 2 weeks, and then at 3-monthly intervals.

Results

Donor/recipient blood groups were identical in all cases. Cold ischaemia times of the donor livers ranged from 6–14 h (median 12 h). The median duration of surgery was 8.5 h (range, 7.3–10 h), with blood loss of 8.3 litres (4.6–14.6 litres). Veno-venous bypass was not used. Intra-operatively, no major changes occurred in the cardiac index or mean arterial pressure in any patient. Postoperatively, there were no technical complications such as bile leak or hepatic artery or portal vein thrombosis, but two patients required a second laparotomy within the first week for clot evacuation.

Following APOLT, the INR and AST fell progressively in all seven patients, with median values at day 7 of 1.4 (range, 1.0–2.4) and 108 IU/l (78–910 IU/l), respectively. In contrast, serum bilirubin concentrations at day 7 post-transplant (median 213 μmol/l; 87–291 μmol/l) were not significantly different from those at day 1 (164 μmol/l; range 64–207 μmol/l) (Fig. 1). During this time, Doppler ultrasonography confirmed patency of the portal vein, hepatic artery and hepatic veins.

Associated with this slow improvement in graft function, there was a high frequency of bacterial infection in the early postoperative period, with a median time to extubation of 9 days (Table 2). Three patients died from sepsis syndrome and associated multiorgan failure within the first postoperative month. Patient 2 was initially extubated on day 14, but required re-intubation 1 week later following the development of bronchopneumonia. Just before her death on day 31, a multiresistant *Klebsiella aerogenes* was isolated from blood cultures. Patient 5 – who was considered not to be eligible for conventional OLT – had high inotrope requirements and a severe metabolic acidosis (arterial pH 7.06) before transplantation. Post-APOLT, he developed bronchopneumonia, with a persistent metabolic acidosis and high inotrope requirements, and lower limb ischaemia. Despite aggressive support, he

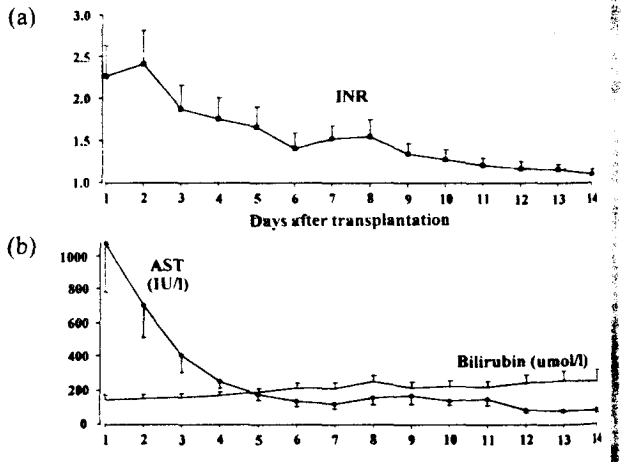

Fig. 1. Postoperative changes in the mean (±SEM) (a) International Normalised Ratio (INR), and (b) serum aspartate aminotransferase (AST) and total bilirubin. The normal values are given in Table 1.

TABLE 2

Clinical outcome and native liver regeneration

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Site of auxiliary graft	Left	Left	Right	Right	Right	Right	Right
% liver cell necrosis in native lobe	60	50	90	80	95	80	50
Days ventilated	11	25	14	9	9	5	10
Minimum INR after transplantation	0.8	1.2	1.0	1.1	2.2	1.0	1.4
Final outcome	Well	Died day 31 (sepsis)	Died day 38 (sudden death)	Well	Died day 9 (sepsis)	Well	Died day 10 (sepsis)
Native lobe regeneration at:							
2 weeks	Partial	Nil	Partial	Partial	Partial	Nil	Not done
3 months	Complete			Partial		Nil	
1 year	Complete			Complete		Nil	
Immunosuppression withdrawal	Complete			Complete		No	

died on day 9 post-transplant. Patient 7 improved clinically in the first postoperative week, but deteriorated with *Aspergillus* pneumonia and haemophagocytic syndrome, and died on day 10.

The four remaining patients also had a relatively complicated postoperative course, with the development of pneumonia requiring prolonged (>1 week) mechanical ventilation in three, oliguric renal failure requiring continuous veno-venous haemodiafiltration in three, and recurrent seizures in one. However, all four patients were successfully extubated, and three were discharged from hospital on days 14, 21 and 42 (Table 2). At the time of discharge on tacrolimus monotherapy, the INR and AST were normal in all three patients. The fourth patient died suddenly on day 38 post-transplant. On the day before her death, she was clinically well with normal graft function. There was no history of heart disease, epilepsy or pulmonary embolism. Post-mortem examination and toxicology screening were non-contributory.

Sequential pathology of the native livers

The resected left native liver lobes in two, and right lobes in five, were available for gross and histological examination. Macroscopically, the changes (zonal confluent or submassive necrosis) were evenly distributed in five patients, whereas the livers of patients 2 and 7 showed large and small nodules of regeneration, respectively, discernible on both the capsular and cut surfaces. Histologically, the nodules corresponded to large macronodular areas of spared parenchyma composed of large hepatocytes arranged in thickened plates. The nodules alternated with broad areas of multiacinar collapse in which approximated portal tracts were surrounded by ductular structures only. The degree of hepatocyte loss in these two cases was estimated to be more than 50% of the total surface area of the sections. In contrast, liver histology in patients 1 and 6 revealed confluent hepatocyte loss in acinar zone 3, with spotty and/or focal cell loss randomly scattered in the rest of the acini, amounting to approximately 60% and 80% cell loss, respectively. Furthermore, there were neoductules and microregenerative nodules in a periportal distribution and, in case 6, multinucleated giant hepatocytes. The livers of patients 3, 4 and 5 with paracetamol-induced necrosis were distinctive in that instead of cell dropout, confluent eosinophilic necrosis was seen and estimated to affect 90%, 80% and 95% of these livers, respectively. In case 4, continuous mantles of enlarged and pale-staining hepatocytes with few mitoses formed thick plates around the portal areas (Fig. 2a). In cases 3 and 5, islands of similar-appearing hepatocytes were present, interrupted by poorly defined ductules composed of small biliary-type epithelial cells seemingly sprouting from the portal periphery. Cholestasis was severe and closely associated with preserved, regenerative parenchyma in the two cases with macroscopic nodules, mild in cases 1 and 6 and inconspicuous in the three with paracetamol-induced necrosis. In these latter three patients, inflammation was sparse and composed predominantly of activated macrophages and neutrophils. In the remaining four cases, the inflammatory cell infiltrate was more dense and mixed cell in composition, affecting predominantly the collapsed areas with some reinforcement in the portal tracts.

At a median of 14 days (range, 9–19 days) post-APOLT, ultrasound-guided needle biopsies of the native and donor liver lobes were performed in six patients; a post-mortem biopsy failed to sample the native liver in patient 7. At this time, four of the six native livers showed evidence of regeneration, with periportal zones of enlarged hepatocytes arranged in thick plates having expanded, and the collapsed areas having shrunken when compared with the hepatectomy specimens (Fig. 2b and 2c). In case 2 – whose resected liver

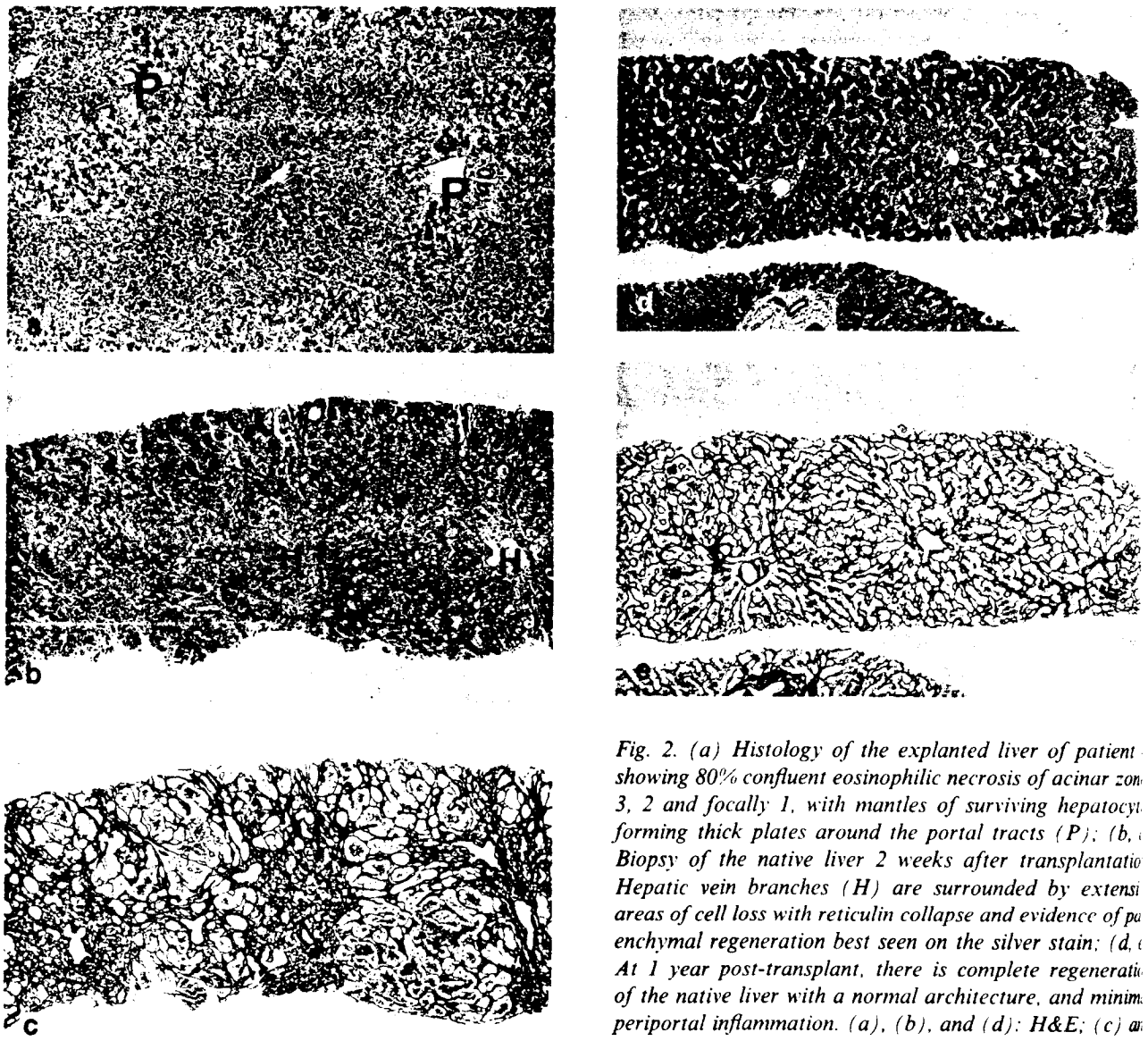

Fig. 2. (a) Histology of the explanted liver of patient showing 80% confluent eosinophilic necrosis of acinar zon 3, 2 and focally 1, with mantles of surviving hepatocyt forming thick plates around the portal tracts (P); (b, Biopsy of the native liver 2 weeks after transplantatio Hepatic vein branches (H) are surrounded by extensi areas of cell loss with reticulin collapse and evidence of pa enchymal regeneration best seen on the silver stain; (d, At 1 year post-transplant, there is complete regeneratio of the native liver with a normal architecture, and minim periportal inflammation. (a), (b), and (d): H&E; (c) an (e): silver stain for reticulin.

had shown regenerative macronodules – the needle had probably sampled a multiacinar collapsed area as the biopsy showed complete cell dropout with ductular structures only. Similarly, the specimen from patient 6 revealed collapsed parenchyma with ductular proliferation. In the last two specimens, there was also a severe inflammatory cell infiltrate.

At 3 months, the three surviving patients underwent repeat biopsies. In patient 1, a good core of native liver tissue showed only mild perivenular reticulin condensation with complete replenishment of the liver parenchyma by hepatocytes of normal appearance, arranged preferentially in two-cell-thick plates. Inflammation had subsided. Nearly complete restoration of the liver parenchyma also occurred in case 4, apart from patchy residual collapse of the reticulin associated with a fe clusters of pigmented macrophages. In case 6, ther were no histological features of regeneration. On th contrary, throughout the specimen the proliferate ductules were more scanty and the inflammatory infi trate more dense than in the week 2 biopsy.

At 1 year, patients 1 and 4 underwent repeat biop sies, which demonstrated near normal liver tissue There was persistence of a few two-cell-thick plates an some prominence of portal areas which contained oc casional mixed inflammatory cells (Fig. 2d and 2e).

Histology of the auxiliary grafts

Concomitant biopsies of the auxiliary grafts wer available in all patients. At 2 weeks, histology revealed

minor, non-specific changes or mild cholangitis in three of the seven, marked cholestasis in two, and severe ischaemic changes in one (post-mortem specimen from patient 5). Patient 1 – who had partial regeneration of the native liver – had histological evidence of moderate cellular rejection in the auxiliary graft, which responded to a 3-day course of intravenous methylprednisolone. Subsequent biopsies demonstrated a progression from acute to chronic rejection in the auxiliary graft, and gradual regeneration of the native lobe, with full regeneration of the native liver seen in the 3-month biopsy. In patient 4, repeat liver biopsies of the auxiliary graft at 1 year post-transplant revealed moderate acute cellular rejection of the auxiliary graft. Tacrolimus was subsequently withdrawn, and at 2 years post-transplant, she remains well with normal native liver function.

Hepatobiliary cholescintigraphy and immunosuppression withdrawal

At 2 weeks and 3 months, the three long-term survivors underwent hepatobiliary cholescintigraphy. In patient 1, an initial week 2 IDA scan had shown partial uptake of the radiolabel by the native liver, although approximately 90% of the tracer was excreted through the auxiliary graft. In contrast, the 3-month IDA scan – performed during continued immunosuppressive therapy – showed almost 100% uptake and excretion by the hypertrophied native lobe. At 1 year post-transplant, immunosuppressive therapy was ceased and the auxiliary graft allowed to atrophy. Two years later, he continues to have normal liver function tests and remains off all immunosuppressive therapy.

In patient 4, the initial two hepatobiliary IDA scans showed little change over a 3-month period. In both studies, there was minimal uptake of tracer in the native left lobe, with a ratio of function in the right to left lobe of approximately 90:10. However, at 1 year – when there was complete histological recovery of the native liver – the corresponding IDA scan also revealed good functional recovery, with a ratio of function of the auxiliary and native lobes of approximately 50%.

In patient 6, there was no functional or histological evidence of native liver regeneration at 2 weeks, 3 months or 1 year. He remains on tacrolimus monotherapy with normal liver function tests and a histologically normal auxiliary graft.

Discussion

Auxiliary partial orthotopic liver transplantation has a number of potential advantages over conventional OLT, but experience of the technique in ALF is limited. In this further series of seven adults with ALF, APOLT was technically successful but more difficult than OLT, with a median duration of surgery of over 8 h and blood transfusion requirements of approximately eight litres. Two patients required a second laparotomy for clot evacuation. However, none developed biliary leaks, or hepatic artery or portal vein thrombosis – important causes of morbidity and mortality in other recent series of APOLT in ALF (17,18).

Despite the low rate of surgical complications, all of the patients made a slow clinical improvement initially, with a high incidence of bacterial sepsis and a median time to extubation of 9 days. Furthermore, the rate of fall in the INR and AST during the first week post-APOLT was slower than that expected following conventional OLT for ALF in our Unit (24,25), while the mean serum bilirubin concentration did not begin to fall until the second week. These findings are similar to those of Boudjema et al. (18). In their series of eight patients with fulminant or subfulminant hepatic failure who underwent APOLT, the mean INR and AST were still above normal values at the end of the first week.

The slow clinical and biochemical recovery seen in the patients suggests that the retained left or right necrotic lobe may have contributed to the development of a "toxic liver syndrome" post-transplant, and predisposed the patients to a higher rate of complications than would be expected following conventional OLT. The mechanisms for such an effect, in patients undergoing auxiliary liver transplantation for ALF, have not been studied. However, in both humans and animal models, ALF is associated with increased amounts of circulating cytokines and nitric oxide (26–28), and impaired neutrophil and Kupffer cell function (29–31). Studies in animal models also suggest that, in ALF, cytokines and activated Kupffer cells are directly hepatotoxic (32–34). These findings may explain, in part, the observation that patients with hepatocellular necrosis temporarily improve after total hepatectomy (35–37). Based on these considerations and our initial experience with left auxiliary grafts, we postulated that an extended right hepatectomy – where more than 60% of the necrotic native liver is removed – may reduce the risks to the patient of an ongoing sepsis syndrome. A related aim was to retain a sufficient quantity of the native left lobe so that, in the event of native liver regeneration, immunosuppressive therapy could be withdrawn. However, our initial results, and those of other investigators (17,18), have not shown a difference in the early postoperative course or overall outcome between patients undergoing a left or right auxiliary transplant, and further studies are required.

In the present study, the major cause of death was related to the development of sepsis syndrome and multi-

organ failure postoperatively, with only four of the seven patients (57%) surviving longer than 1 month after transplantation. The previously reported experience of APOLT in ALF has suggested a 1-year survival rate of 69–75% (17,18) – similar to that following conventional OLT (1–3). However, it is possible that these reported survival rates after APOLT represent a selection bias. In these series (17,18), over 80% of patients were <40 years of age, and approximately half of the patients had viral hepatitis or paracetamol hepatotoxicity – favourable prognostic factors in ALF (38).

Age, the jaundice-to-encephalopathy time, and the aetiology of liver failure – indicators of survival in ALF (4,23) – may also be predictive factors for native liver regeneration after APOLT. In the European series of orthotopic (n=23) or heterotopic (n=7) auxiliary liver transplantation in patients with ALF (17), 13 of 19 survivors (68%) regained normal native liver function, and ceased immunosuppression, after a median of 11 months. All five children in this series had complete regeneration within a few weeks. In contrast, three of four patients over the age of 40 developed bridging fibrosis or cirrhosis within the native liver. Furthermore, complete native liver regeneration occurred in 7/8 (87%) patients with hyperacute liver failure and 5/5 (100%) with subacute liver failure, but in only 3/9 (33%) of patients with a jaundice-to-encephalopathy time of 8–28 days. All three patients with Ecstasy or halothane hepatotoxicity, two of six patients with fulminant hepatitis B, but none of five patients with hepatitis A or paracetamol-induced liver failure, developed fibrosis or cirrhosis within the native liver.

To assess the percentage of viable hepatocytes and the presence or absence of fibrosis within the necrotic native liver, some investigators have examined frozen section biopsies, obtained intra-operatively, before proceeding to APOLT (17,18). However, in the series by Chenard-Neu et al. (17), nine of 10 patients with >90% hepatocellular necrosis, and two of our patients with 60–80% hepatocyte necrosis, had complete histological and functional recovery of the native liver. Thus, a high proportion of surviving hepatocytes within the necrotic parenchyma is not a prerequisite for native liver regeneration following APOLT (17,39). In fact, our results, and those of Chenard-Neu et al. (17), suggest that the presence of macroscopic regeneration nodules within a small, necrotic native liver, predicts the development of fibrosis or cirrhosis after APOLT.

The major advantage of auxiliary liver transplantation over conventional OLT is the potential for native liver regeneration. The benefits to the patient of eventual immunosuppression withdrawal include a reduced incidence of drug-related side effects and neoplasia, and monitoring requirements (40). Based on these considerations, and uncontrolled evidence that the mortality associated with APOLT and conventional OLT is similar, further studies of APOLT in ALF seem warranted. In our opinion, the evidence to date suggests that APOLT should only be considered in young patients (age <40–50 years) who are stable pre-operatively, with no evidence of sepsis syndrome or raised intracranial pressure, and who do not require large amounts of inotropic support. Patients with ALF secondary to Ecstasy, halothane or other idiosyncratic hepatotoxins, and possibly those with macroscopic regeneration nodules within a small, necrotic liver, appear to be more likely to develop fibrosis/cirrhosis after APOLT. Conversely, those with fulminant hepatitis A or hyperacute liver failure due to paracetamol hepatotoxicity, represent favourable prognostic categories and may be the best groups to consider for APOLT.

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