Cell Transplantation, Vol. 15, Supplement 1, pp. S105–S110, 2006
Printed in the USA.

0963-6897/06 $90.00 + .00
E-ISSN 1555-3892
www.cognizantcommunication.com

Hepatocyte Transplantation: Clinical Experience and Potential for Future Use

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Hepatocyte transplantation has been proposed as a method to support patients with liver insufficiency. There are three main areas where the transplantation of isolated hepatocytes has been proposed and used for clinical therapy. Cell transplantation has been used: 1) for temporary metabolic support of patients in end-stage liver failure awaiting whole organ transplantation, 2) as a method to support liver function and facilitate regeneration of the native liver in cases of fulminant hepatic failure, and 3) in a manner similar to gene therapy, as a "cellular therapy" for patients with genetic defects in vital liver functions. We will briefly review the basic research that leads to clinical hepatocyte transplantation, the published clinical experience with this experimental technique, and some possible future uses of hepatocyte transplantation.

Key words: Hepatocyte transplantation; Clinical experience; Future use

INTRODUCTION

There are more than 20,000 patients awaiting liver transplantation in the US. On average over a 1-year period, organs become available for less than 1/3 of them. Hepatocyte transplantation has been proposed as a method to support liver function in acute or chronic hepatic insufficiency and as a "cell therapy" for metabolic diseases in the liver (12,14,23,34,44). Numerous studies in animal models clearly indicate that hepatocytes transplanted into the spleen or the portal vein display normal hepatic function and can function for the lifetime of the recipient (16,18,27,38). Hepatocyte transplantation has been shown to dramatically improve survival in animals with acute liver failure induced by *d*-galactosamine (22,29,41,47), 90% hepatectomy (7,21), or ischemic liver injury (48). Transplantation of hepatocytes into the spleen was shown to significantly improve or correct prothrombin time (PT), serum albumin, and bilirubin levels and hepatic encephalopathy and survival in a rat model of terminal end-stage cirrhosis (1,5,32). Metabolic defects in bilirubin metabolism, albumin secretion, copper excretion, familial intrahepatic cholestasis, and tyrosinemia have been corrected by hepatocyte transplantation (8,15,18,20,24,30,35,37,49). By about 1990, the question was not if hepatocyte transplants could be an effective treatment for liver disease, but how could this experimental treatment be translated into a clinical setting (17,28,45).

We review published data on over 25 transplants in patients with a variety of liver diseases (4,9,11,13,19,31, 40,42,45,46). Human hepatocyte transplants mirror the results of animal experimentation and indicate that hepatocyte transplants can lower ammonia levels, increase cerebral perfusion pressure, and decrease intracranial pressure in patients with acute liver failure and affect an overall increase in patient survival (4,42,45,46). As with the animal studies, hepatocyte transplants in the clinics restore biochemical function in liver-based metabolic disease. Partial corrections of bilirubin metabolism (2, 13), a urea cycle disorder (19), and glycogen storage disease, type 1 (31), an inborn error in fatty acid metabolism (40), a clotting factor deficiency (9) have been reported. While still experimental, these promising early results suggest that hepatocyte transplants could be an inexpensive and effective therapy for liver disease.

There are few options for the treatment of severe liver disease other than orthotopic liver transplantation (OLTx). Although it is currently the preferred treatment for many end-stage liver diseases, OLTx is a costly surgery with a high incidence of surgical and other medical complications such as infections. Whole organ trans-

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plant requires in most cases life-long and expensive immunosuppressive therapy. Untoward reactions associated with immunosuppressive drugs include impairment of renal function, hyperlipidemia, and increased incidence of tumors with prolonged use. In any given year, there are nearly five times as many people who would benefit from whole liver transplantation than there are organs available. Because organs are not always available when a patient requires them, timing of organ availability is a critical concern of those awaiting OLTx. Hepatocyte transplantation (HTx) has some theoretical advantages in certain limited cases. Because HTx is usually performed by infusion of a limited number of cells into the vascular supply to an organ such as the spleen or liver, HTx is less invasive, less costly, and has been associated with fewer and less serious complications. Timing is less critical for cell transplants than whole organ transplants because hepatocytes can be cryopreserved and used when needed. As shown in the diagram in Figure 1, we believe that there are three patient categories where cell transplantation may be useful. Due to organ shortages, OLTx may not available at the time needed for acute liver failure or acute decompensation of chronic liver disease. HTx may be applied in such a case to provide temporally support to bridge to OLTx (Category I). Patients who develop acute hepatic failure may receive temporary support of hepatic function by freshly isolated or even previously cryopreserved hepatocyte transplantation (Category II). When the patient's native liver regenerates sufficiently to allow recovery from the acute event, immunosuppression can be discontinued. It is theoretically possible that some patients suffering from congenital metabolic disease may receive sufficient support of metabolic function from transplanted cells so that they would no longer require whole organ replacement. However, to date no patients have experienced a complete clinical correction of the symptoms of their metabolic disease by cell transplantation alone. Within this paradigm cell transplantation should not necessarily be seen as a replacement for OLTx, but rather as an additional therapeutic option for these patients.

Although not yet realized for clinical transplants, it may be possible to increase the numbers of human hepatocytes available for transplantation if conditions could be identified that would allow their ex vivo expansion in culture. With future progress, it is likely that hepatocytes derived from stem cell sources will become available for clinical transplants. Because of the advantages, HTx is being considered as a viable therapeutic intervention in patients with severe liver disease.

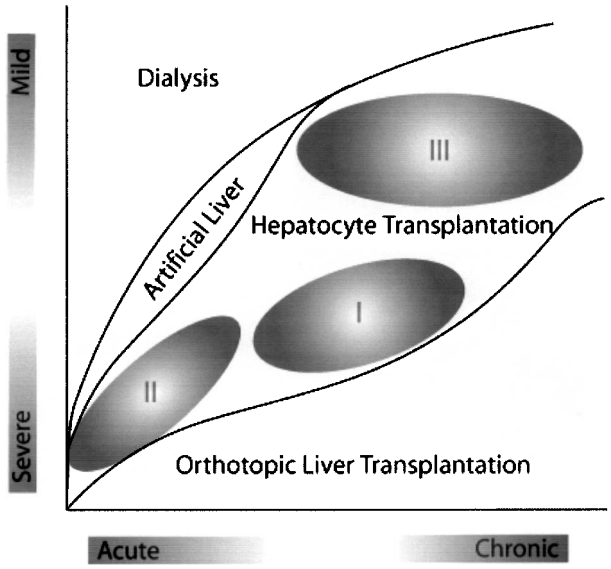

Figure 1. Application of hepatocyte transplantation. (I) Bridge to whole organ transplantation. Hepatocyte transplantation supports liver function in cases of acute liver failure and in end-stage liver failure following a chronic disease such as cirrhosis. (II) Hepatocyte transplantation can provide temporary support until the native liver recovers from acute fulminant hepatic failure. Freshly isolated or well-characterized cryopreserved hepatocytes may be used. (III) Cell therapy for metabolic disease. Partial or complete correction of hepatic function may be provided by hepatocyte transplantation alone. Even partial corrections of liver function should lead to an improvement of the patient's quality of life.

HEPATOCYTE TRANSPLANTATION FOR ACUTE LIVER FAILURE AND ACUTE DECOMPENSATION OF CHRONIC LIVER DISEASE

There are several reports of the use of isolated hepatocyte transplantation to support liver function in cases of acute liver failure and in end-stage liver failure following a chronic disease such as cirrhosis. As summarized in Table 1, hepatocyte transplants were shown to be effective treatments in experiments conducted with several models of acute or chronic liver failure in experimental animals (1,5,7,21,22,29,32,41,47,48). These results with animal models have lead to attempts to support patients with acute or chronic liver failure by HTx

Table 1. Acute Hepatic Failure Corrected by Hepatocyte Transplantation

Fulminant hepatic failure due to: 90% hepatectomy, or galactosamine, carbon tetrachloride, thioacetamide, or fas ligand administration
Ischemia/reperfusion injury
Acute decompensation of chronic liver failure

(4,11,17,28,42,46). Results presented in Table 2 summarize some of the data from patients receiving hepatocyte transplants (10,11,43–46). In 20 patients listed for whole organ transplantation, HTx was used as a bridging technique to provide and support liver function while the patients were awaiting OLTx. The results indicate that there were 11 survivors and 7 deaths in this group. An additional 4 patients were included as controls for the cell transplant procedure. Controls were those patients whose families declined the experimental treatment of those for whom the correct blood type of cells were not available at the time the patient presented. As indicated in Table 2, there were no survivors in the control group and over 60% survival in the treatment group receiving HTx. These preliminary studies suggest that those patients receiving HTx have a survival advantage compared to those who do not. These studies suggest that HTx may have a role in support of liver function in patients awaiting OLTx.

HEPATOCYTE TRANSPLANTATION TO SUPPORT LIVER FUNCTION AND FACILITATE REGENERATION OF THE NATIVE LIVER

The goal of the studies described in Table 2 was not to prevent OLTx, but to merely provide temporary liver support to patients awaiting OLTx and to help keep them alive long enough to receive OLTx. However, in two of the cases, the patients recovered from acute liver failure without ever having to receive the OLTx. The first case was a patient with acute hepatic failure perhaps induced by a combination of hepatitis B virus and illicit drug use (11). A second patient suffered from acute hepatic failure following acetaminophen intoxication (10). In both cases the patients recovered following the transplantation of hepatocytes and the improvement was sufficiently rapid that they were subsequently removed from the transplant list. Full recovery took at least 2 weeks following the hepatocyte transplantation. Soriano et al. (42) reported the complete recovery of a pediatric patient suffering from fulminant hepatic failure of unknown etiology following the support of liver function by hepatocyte transplantation, and a recent preliminary report indicates that one additional adult patient has been supported by HTx alone in a case of fulminant hepatic failure due to mushroom poisoning (36). These reports are important for several reasons. If a liver had been available each of these patients would have received the costly OLTx and would have likely needed life-long immunosuppression. As indicated by Fisher et al. (11), although donor cells could be identified following the transplant, most of the cells in the recipient's liver 3 months following HTx were native. It was suggested that the HTx provided adequate liver support to keep the patient alive to provide time for the native liver to regenerate. Because the native liver had regenerated, by 3 months posttransplant, immunosuppressive therapy could be discontinued. These case reports indicate that HTx can be an effective treatment for fulminant hepatic failure and that in certain cases OLTx and life-long immunosuppression can be obviated by cell transplant alone.

Table 2. Survival of Patients Receiving Hepatocyte Transplantation as a Bridge to Whole Organ Transplantation

7 deaths, 3.5 ± 2.3 days
11 survivors, OLT 5 ± 4 days
Controls receiving no cell transplant (no survivors, death at 2.8 ± 2.5 days
2 Patients recovered without OLT

HEPATOCYTE TRANSPLANTATION FOR METABOLIC LIVER DISEASE

As summarized in Table 3, a number of animal models have been discovered or created to investigate genetic deficiencies in liver function. All of those listed have also been the focus of HTx studies directed to determine if cell transplantation alone could correct the clinical symptoms of the disease. In each case, at least partial corrections of these diseases could be attained by cell therapy. Because of the relative success in the animal models, HTx was also investigated in patients with similar defects in liver function. The most successful to date was the partial correction of a pediatric patient with Crigler-Najjar (13), a defect that is characterized by the presence of high levels of circulating bilirubin resulting from the absence of the enzyme responsible for the con-

Table 3. Metabolic Liver Diseases Treated by Hepatocyte Transplantation

Tyrosinemia type 1 (fah)
Analbuminemia
Wilson's disease (Cinnamon rat)
Crigler-Najjar, Gunn rat, CN-type 1
Ornithine transcarbamylase deficiency, CPS (urea cycle defect)
Ascorbic acid deficiency (ODS rat)
Familial hypercholesterolemia
Uric acid metabolism (Dalmation dog)
Hemophilia, factor 7
Glycogen storage disease
Dubin-Johnson syndrome, (MRP2 deficiency)
Progressive familial intrahepatic cholestasis (PFIC, MDR3)

jugation of bilirubin in the liver. Over the next several months following HTx there was a steady and eventual 60% decrease in bilirubin levels. Following HTx, bilirubin diglucuronide conjugates could be detected in the bile. Because these conjugates could only be produced by the donor liver cells this was taken as direct evidence of the integration of donor hepatocytes into the liver, linkage of the donor cells to recipient's biliary tree, and the long-term function of the transplanted cells. A recent report shows a similar correction of a second patient with Crigler-Najjar Syndrome, type 1 (2). Cell transplants were also conducted in patients with ornithine transcarbamylase (OTC) deficiency, a severe urea cycle disorder that prevents the metabolism and elimination of ammonia by the liver (19,45). In OTC patients, dietary protein is severely restricted to prevent the hyperammonemia that accompanies the breakdown of amino acids. For several weeks following hepatocyte transplantation, the patient could be maintained on a full protein diet while being treated with only an oral ammonia scavenger, suggesting that the cell transplantation could provide the liver with the capacity to metabolize ammonia. It was thought that the patient eventually rejected the donor hepatocytes because of extremely low levels of immunosuppressive drugs administered to the neonatal recipient, but the results suggest that cell transplantation alone might provide sufficient capacity to metabolize the ammonia produced from a standard protein diet. Transplants of additional patients for OTC and other urea cycle deficiencies should be considered.

There are other reports of the treatment of metabolic liver diseases in patients by hepatocyte transplants. Muraca et al. (31) reported the treatment of glycogen storage disease, type 1, by hepatocyte trasnplantation. The authors reported that following HTx, the patient displayed a substantial improvement in the ability to maintain blood glucose between meals and sustained higher glucose levels with meals. Sokal et al. (40) reported the use of HTx in a patient with infantile Refsum disease, an autosomal recessive inborn error in peroxisome metabolism of very-long chain fatty acid, bile acid metabolism, and pipecolic acid catabolism. Over the next year following HTx, they reported a substantial improvement in the metabolism of fatty acids, a reduction in circulating pipecolic acid and bile salts levels, and significant increased weight and muscle gain. A recent report from Dhawan et al. (9) summarizes the use of hepatocyte transplantation to treat a liver-based metabolic disorder characterized by a severe deficiency in the production and secretion of the coagulation factor VII. Over the next several months following HTx the requirement for exogenous factor VII diminished to approximately 20% of that required prior to HTx. These results once again support the idea that the transplantation of isolated hepatocytes is sufficient to provide partial correction of genetic defects in liver function.

HEPATOCYTE TRANSPLANTATION CHALLENGES AND FUTURE DIRECTIONS

In addition to acute liver failure and metabolic disease patients, hepatocyte transplantation has been shown to significantly improve liver function and survival in a rat model of chronic liver failure (1,5,32). Anecdotal data exist to suggest that human patients suffering from end-stage hepatic failure following chronic cirrhosis may benefit from hepatocyte transplantation as well (44). With millions of patients currently experiencing chronic liver failure associated with cirrhosis and millions more expected to develop cirrhosis because of chronic hepatitis B or C, the need for additional therapies to support liver function in patients with cirrhosis is critical. Although difficult to design and conduct, HTx should be thoroughly evaluated as a possible support therapy in cirrhosis.

The single most important factor preventing the use of hepatocyte transplants in additional medical centers is the limited availability of hepatocytes. The normal source of cells for hepatocyte transplants are livers with >50% steatosis, vascular plaques, or other factors that render the tissue unsuitable for whole organ transplantation (4,11,13,19,31,33,42,43,45,46). The isolation of viable and useful cells from discarded organs has made possible the small "proof of concept" studies in humans. A wider use of hepatocyte transplants will not be possible until alternative sources of cells are found. Xenotransplants (32), immortalized human hepatocytes (5,21,50, 51), and stem cell-derived hepatocytes (3,6,25,26,39) have been proposed as alternative sources of cells for clinical transplants. While all options have merit, it is likely that stem cell-derived hepatocytes will be a significant source of cells for future hepatocyte transplants.

Over 20 years of research on the use of hepatocyte transplantation in animal models of liver failure and liver-based metabolic disease have shown that HTx is a safe and effective method to support liver function. In many cases of metabolic liver disease, cell transplantation alone could provide sufficient liver function such that the clinical symptoms of the disease were greatly reduced or eliminated. Studies with human hepatocyte transplantation in patients with acute or chronic liver failure and genetic defects in liver function show similar results. In virtually all cases, following HTx there could be documented a clinical improvement in the condition of the patient. While all of this is encouraging, there are still no reports of complete corrections of any metabolic disease in patients by HTx alone, and the long-term function of human hepatocytes following transplantation has not been determined. There are currently no pub-

lished reports that can document sustained clinical improvement in a metabolic disease patient past 2.5 years. This is somewhat surprising, because it is believed from studies with animals that donor hepatocytes transplanted into the spleen or the liver function for the lifetime of the recipient and participate in normal regenerative events. The failure to detect long-term function of transplanted hepatocytes in the clinical setting may be due to the rejection of the allogeneic cells or perhaps through the eventual senescence of the transplanted cells. Future work with carefully monitored transplant and immunosuppression protocols will be needed to determine if either or both of these mechanisms contribute to the eventual loss of hepatocyte function observed in the clinical transplants conducted to date. Still the initial success of the HTx from different laboratories in several different countries and the close ties and cooperation that have developed between investigators at the different transplant centers should provide considerable hope that the technology can be improved over its current state and implemented at additional transplant centers with relative ease.

ACKNOWLEDGMENT: Supported in part by NIH/NIDDK DK 92310.

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