PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

WJG, 1999 August; 5(4):286-288
World Journal of Gastroenterology
 ISSN 1007-9327

Invited Commentary

Bioartificial liver support for fulminant hepatic failure

Robert S. Brown, Jr.[1] and Howard J. Worman[2]

See article on page 308

ORIGINAL ARTICE

Effects of a bioartificial liver support system on acetaminophen-induced acute liver failure canines.

MAJOR POINTS OF THE COMMENTED ARTICLE

Investigations of bioartificial liver support systems are rather novel in mainland China. In this issue of the *World Journal of Gastroenterology*, Xue *et al*[1] report on the safety and efficacy of a bioartificial liver support system developed in Hong Kong (TECA-I, TECA Ltd.) in dogs with fulminant hepatic failure. In the TECA-I bioartificial liver system, whole blood is perfused through hollow fiber tubes containing porcine hepatocytes. These investigators induced acute hepatocyte necrosis, as evidenced by elevations in the serum aminotransferase activities and subsequent histological examinations, by administering overdoses of acetaminophen (multiple injections of 115mg/kg). Fulminant hepatic failure with concomitant elevations in the serum ammonia concentrations resulted. Six of 9 dogs treated with TECA-I bioartificial liver system survived for more than 30 days, suggesting full recovery of hepatic function. In contrast, 10 dogs treated with either intravenous glucose or with arginine, glutamic acid and branch chain amino acids all died within 36 hours after treatment. These results represent an initial step towards clinical trials of a bioartificial liver suppor t system in China.

COMMENTARY

Fulminant hepatic failure

The liver can fail acutely with rapid loss of hepatocyte function. In the otherwise healthy individual, the presentation is dramatic and can cause mental status alterations, coma and a rapidly deteriorating course that leads to death. The term fulminant hepatic failure is used to describe the presence of hepatic encephalopathy in liver disease of short duration[2].

There are several causes of fulminant hepatic failure including viral infections, drugs (overdose of acetaminophen is one example[3]), toxins, hemorrhagic shock, congestive heart failure, severe fluid depletion, sepsis and various metabolic derangements. In some hospitalized patients, the cause of fulminant hepatic failure may never be established. This may be because the patient deteriora tes too rapidly for diagnostic testing to be completed or because the precipitating event, such as ingestion of a toxin or overdose of a drug, is not witnessed or reported.

Individuals with fulminant hepatic failure will have various signs and symptoms of liver dysfunction. As already mentioned, hepatic encephalopathy, with elevated serum ammonia concentrations, is part of the diagnosis. Increased intracranial pressure and cerebral edema can lead to irreversible brain damage and is a common cause of death. All patients are jaundiced with significantly elevated serum bilirubin concentrations. The serum prothrombin time is elevated and abnormal bleeding may result. Renal failure from acute tubular necrosis or hepatorenal syndrome often complicates the picture. Disseminated intravascular coagulation, infections, sepsis and respiratory failure may also occur. In contrast to individuals with cirrhosis, complications of portal hypertension such as ascites and bleeding esophageal varices are generally not significant problems in patients with fulminant hepatic failure.

In fulminant hepatic failure, aminotransferase activities may be markedly elevated as a result of the massive hepatocyte necrosis that occurs after a sudden insult to the liver. This is especially with sudden, massive hepatocyte necrosis seen in acetaminophen overdose[3] and shock liver[4]. Serum aminotransferase activities may only be elevated for a few days and then return to normal or near normal, despite the presence of severe hepatic dysfunction[3,4]. Therefore, their normalization does not necessarily indicate an improvement in

[1]Departments of Medicine and of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[2]Departments of Medicine and of Anatomy and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, NY 10032 USA
Correspondence to: Dr. Robert S. Brown or Dr. Howard J. Worman, Department of Medicine College of Physicians and Surgeons, Columbia University, 630 West 168th Street, 10th Floor, Room 508, New York, NY 10032, USA
Tel. (212)305-8156, Fax. (212)305-6443
Email: hjw14@columbia. edu(Dr. Worman); rb464@columbia.edu (Dr. Brown)
Received 1999-07-14

condition because they cannot remain elevated if no more hepatocytes are left to die.

Treatment

Hepatic stem cells (oval cells), which may originate in the bone marrow[5], and/ or hepatocytes can divide and are capable of repopulating a liver in which up to 90% of the hepatocyte mass is destroyed. In fulminant hepatic, complete recovery is therefore possible if the cause of hepatocyte death is reversed, adequate supportive care is provided, and cerebral edema does not occur. Unf ortunately, many or most patients succumb before hepatocytes can regenerate to restore adequate liver function.

The treatment goal in fulminant hepatic failure is to keep the patient alive and free of serious complications either until: ① liver function spontaneously recovers or ② emergency liver transplantation, which is effective in cases of fulminant hepatic failure[6], can be performed. A significant advance in treatment of it would be the ability to "buy time" either until adequate hepato cyte regeneration occurs and the patient recovers or until a donor organ becomes available for transplantation. If temporary liver support could be provided, the need for emergency transplantation may even be obviated as adequate function may eventually return in the damaged liver.

Bioartificial liver support

One way to "buy time" in fulminant hepatic failure bioartificial liver support[7]. This is achieved with biomechanical devises in which plasma or blood is subjected to living hepatocytes extracorporeally. Several studies, including one of the first from China[1] reported in this issue of the *World Journal of Gastroenterology*, have reported experimental trials of bioartificial liver support systems in animals with fulminant hepatic failure.

In the United States and Europe, a few trials of bioartificial liver support devices have been conducted in human subjects. Several others are currently in progress. Clinical experience with bioartificial liver systems has focused on two different types of devices. The first, developed by Demetriou and colleagues[8] at Cedar Sinai Medical Center in Los Angeles, is now manufactured by Circe Biomedical (Lexington, MA). This device uses plasma perfusion and requires plasma separation with the Cobe Spectra (Lakewood, CO). The plasma is passed through a charcoal column, warmed and oxygenated and then passed through a hollow fiber cartridge containing approximately 40 grams of porcine hepatocytes. The hepatocytes are cryopreserved and thawed with a viability greater than 70% prior to use. Treatments are for 7 hours per day. The second device, initially developed by Sussman and colleagues[9] at Baylor in Houston with the trade name Hepatix, is now being manufactured by VitaGen (La Jolla, CA). This device uses whole blood perfusion and a transformed human cell line, C3A cells, in its hollow fiber cartridge. This device can be used continuously. Both devices use venovenous access via a standard dual lumen dialysis catheter usually placed in the femoral vein.

The advantages of whole blood perfusion are simplicity, less personnel costs (no pheresis nurse required), the ability to use devices in parallel (e.g. continuous venovenous hemofiltration), ability to use the device continuously and lower volume loads. Plasma separation requires the use of large volumes of citrate resulting in both a volume load as well as a risk of hypocalcemia, which often requires continuous calcium infusion. It is also more labor intensive and requires an extra device. However, plasma separation does result in less hemolysis and thrombocytopenia and avoids the need for systemic heparin administration. Finally there is a potential advantage to the lack of cellular components in the cartridge, which could lead to immune activation. Overall the major advantages of whole blood perfusion, continuous use, devices in parallel, and lower volume loads makes this method preferable.

The ideal cells to populate a liver support system would be human liver cells. However, until human liver stem cells can be isolated reliably, this remains limited by shortage. Transformed human liver cells will make human proteins, are able to multiply, and will pack more densely in hollow fiber devices allowing for increased hepatocyte mass (approximately 100 grams). However, liver function is often variable and reduced compared with primary hepatocytes, particularly with regard to cytochrome p450 activity and glucuronidation[10]. Finally there are concerns regarding tumorigenic risk, particularly in patients who receive a liver transplant and subsequent immunosuppression. Non-human hepatocytes will have normal liver function but will make non-human proteins. There are also concerns regarding antibody responses to xenogenic tissues and potential zoonoses. Most research to date has used porcine hepatocytes due to availability of adequate mass of cells. The concerns regarding porcine endogenous retroviruses appear theoretical; no porcine retroviral sequences have been detected by reverse transcription-polymerase chain reaction in patients treated with the Circe device (Chris Stevens, MD, personal communication). Finally early clinical data has supported efficacy of porcine hepatocyte-based devices, including lowering intracranial hypertension in acute liver failure.

Phase I data on the circe liver assist system have been very encouraging. In a group of patients

with acute liver failure ($n = 18$) or primary non-function of a transplanted liver ($n = 3$), survival was 90% with one patient having spon taneous recovery[8]. Importantly, patients treated with the device had l ower intracranial pressure readings during treatment. Among patients with acute on chronic liver dysfunction ($n = 10$), results were worse with high mortality[8]. Thus the device is currently being tested only for patients with acute liver failure or primary non-function of a transplanted liver in a multi-center phase II/III randomized controlled clinical trial at liver transplant centers in the United States and Europe. This trial will likely complete enrollment in the next year. The device from VitaGen was previously tested under the trade name Hepatix in a non-controlled Phase I trial and a pilot controlled trial. In the Phase I trial 11 patients with acute liver failure were treated with 6 deaths, 1 spontaneous recovery and 4 transplants[9]. Neurologic or biochemical improvement was seen in 10 of 11 patients treated, but 5 of the 6 deaths were due to intracranial hypertension. In the controlled trial (n =24), there was no survival benefit seen either in transplant patients (78% survival among controls, 75% with the device, $n = 17$) and 25% and 33% respectively among non-transplant patients[11]. This device is currently undergoing further phase I testing in the United States.

In summary, early clinical evidence supports some efficacy for bioartificial liver support systems in fulminant hepatic failure. Future discoveries in basic cell biology will undoubtedly lead to superior systems. Of those currently available, the porcine hepatocyte system is further developed. Additional research and human clinical trials are needed to define the best cell lines, method of perfusion (whole blood *vs* plasma) and methods to expand the clinical indications for bioartificial liver support systems.

REFERENCES

1 Xue YL, Zhao SF, Zhang ZY, Wang YF, Fi XJ, Huang XQ, Luo Y, Huang YC, Liu DG. Effects of a bioartificial liver support system on acetaminophen-induced acute liver failure canines. *World J Gastroenterol*, 1999;5:308-311

2 Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant hepatic failure: definitions and causes. *Sem Liver Dis*, 1986;6: 97- 106

3 Prescott LF, Wright N, Roscoe P, Brown SS. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. *Lancet*, 1971;i:519-521

4 Gitlin N, Serio KM. Ischemic hepatitis: widening horizons. *Am J Gastroenterol*, 1992;87:831-836

5 Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS, Greenberger JS, Goff JP. Bone marrow as a potential source of hepatic oval cells. *Science*, 1999;284:1168-1170

6 Ascher NL, Lake JR, Emond JC, Roberts JP. Liver transplantation for fulminant hepatic failure. *Arch Surg*, 1993;128:677-682

7 Sussman NL, Gislason GT, Kelly JH. Extracorporeal liver support. Application to fulminant hepatic failure. *J Clin Gastroenterol*, 1994;18:320-324

8 Watanabe FD, Mullon CJ, Hewitt WR, Arkadopoulos N, Kahaku E, Eguchi S, Khalili T, Arnaout W, Shackleton CR, Rozga J, Solomon B, Demetriou AA. Clinical experience with a bioartificial liver in the treatment of severe liver failure: a phase I clinical trial. *Ann Surg*, 1997;225:484-491

9 Sussman NL, Gislason GT, Conlin CA, Kelly JH. The hepatix extracorporeal liver assist device: initial clinical experience. *Artif Organs*, 1994;18:390-396

10 Nyberg SL, Remmel RP, Mann HJ, Peshwa MV, Hu WS, Cerra FB. Primary hepatocytes outperform Hep G2 cells as the source of biotransformation functions in a bioartificial liver. *Ann Surg*,1994; 220:59-67

11 Ellis AJ, Hughes RD, Wendon JA, Dunne J, Langley PG, Kelly JH, Gislason GT, Sussman NL, Williams R. Pilot controlled trial of the extracorporeal liver assist device in acute liver failure. *Hepatology*, 1996;24:1446-1451

Edited by MA Jing-Yun