Support of the acutely failing liver: state of the art.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1191422/

Cited in:

Ann Surg. 1998 Jul; 228(1): 14–15.

Support of the acutely failing liver: state of the art.

A A Demetriou

Abstract

Severe acute liver failure results in massive physiologic derangement and high mortality.1 There is a need to support the failing liver until it either recovers or is replaced. Major obstacles facing development of a rational therapeutic strategy include: lack of understanding of the pathophysiology of liver failure, heterogeneous patient populations with multiple disease etiologies and confusing classifications, lack of markers of global liver dysfunction, lack of accurate stratification of the severity of liver failure, lack of reliable outcome predictors, unclear treatment end-points and inexact definition of the role and timing of liver transplantation in treating the disease. Advances in critical care have improved outcomes in severe acute liver failure. Introduction of urgent orthotopic liver transplantation for fulminant hepatic failure (FHF) has significantly reduced mortality2; it is limited, however, by a lack of organs and high cost. An effective treatment is needed to buy time until the native liver regenerates and recovers from acute injury without a need for a transplant. Two major experimental approaches have been used to support the acutely failing liver: 1) Hepatocyte transplantation; 2) Extracorporeal liver support. Two manuscripts published in this issue of the Annals of Surgery by Roger et a13 and Kim et al,4 represent these approaches and demonstrate the progress made in this field. At the same time, they suffer from the same limitations that have plagued previous work in this area and have limited clinical application of emerging therapies.

HEPATOCYTE TRANSPLANTATION The manuscript by Roger et a13 describes a technique of hepatocyte implantation in the peritoneal cavity. Hepatocytes have been transplanted within fibers, using a semipermeable membrane technology to immuno-isolate them. The authors used an experimental small animal model of liver insufficiency (90% partial hepatectomy) and demonstrated significant improvement in animal survival. Several years ago, using a similar animal model, we demonstrated that transplantation of allogeneic hepatocytes in the peritoneal cavity without encapsulation, produced a similar improvement in animal survival.5 It appears that in this animal model a short period of metabolic support by transplanted cells can improve survival and prevent hypoglycemia, the major cause of early death. The need for membrane tech14 nology for cell immuno-isolation is therefore not clear in this animal model. A significant limitation of this study and our own, is the need for cell transplantation several days before 90% hepatectomy, to allow cell engraftment and expression of hepatocyte function. This limits potential clinical usefulness in FHF. The most exciting part of the work of Roger et a13 is the apparent ability of the technique to immuno-isolate xenogeneic cells. In general, this is an interesting technology representing an advance

in the field. It could prove to be more useful for treating genetic defects of liver function where a small number of transplanted cells can correct an underlying genetic defect, rather than in the treatment of severe acute liver failure.

EXTRACORPOREAL LIVER SUPPORT The authors (Kim et a14) describe an interesting biodegradable polymer serving as a scaffold for hepatocytes and tested its function and viability in vitro. This system is an attempt to create a more physiologically and anatomically correct liver in vitro consisting of both parenchymal and nonparenchymal cells. This approach is similar in some respects to that of Gerlach et al.6 The technical challenges facing this technology are formidable. An extracorporeal system has to be simple to be clinically useful and commercially viable. Devices like this one, although they more faithfully reproduce liver architecture, are complex and make "scale up" for clinical use problematic. Additionally, they increase the cost due to the need for continuous culture rather than using cell cryo-preservation techniques. Another potential technical problem is the inclusion of nonparenchymal cells in the system which, although may improve device function, increases antigenicity. This becomes an important issue with repeated use of the device. However, the technology is promising and the system needs to be tested in small and large animals. If the technical issues are resolved, it could represent a significant contribution to the field. The excellent work presented in the two manuscripts published in this issue of the Annals of Surgery3'4 is representative both of the major progress made in this field and the critical issues that need to be resolved to allow transfer of these exciting new technologies from the laboratory to the bedside. In the field of extracorporeal liver support in the United States in the past year, there was only one active clinical trial of a liver support system containing biologic components. It was a phase I clinical trial of a Bioartificial Liver (BAL) system we developed containing cryopreserved microcarrier-attached porcine hepatocytes and charcoal. The Bioartificial Liver was used to treat severe acute liver failure due to: 1) Fulminant hepatic failure (FHF; n = 24) and 2) Primary nonfunction (PNF; n = 3) after liver transplantation. Patients underwent plasma separation and subsequent plasma perfusion through the Bioartificial Liver (Hepat Assist 2000, Circe Biomedical, Lexington, MA) for 6-hour treatment periods, up to five treatments. In Group I, 18 patients were successfully bridged to transplantation (with one death 7 days postoperatively); 5 patients recovered without need for transplant; 1 patient with ischemic FHF after necrotizing hemorrhagic pancreatitis recovered from liver failure and died 3 weeks later from complications of pancreatitis. In Group 11, all three patients were successfully bridged to transplant and recovered. Patients in both groups tolerated the treatments well and survivors had full neurologic recovery. Significant biochemical, physiologic, and neurologic improvements were noted. The Phase I trial has been completed. After evaluation of the safety data, especially the risk of transmission of porcine endogenous retrovirus to patients, by the appropriate regulatory agencies, we expect to initiate a Phase 11/HI of the trial to determine efficacy in a controlled, multi-center study. Extracorporeal liver support is finally reaching the clinical setting. The challenge is to develop simple systems meeting regulatory requirements for safety, which will be proven effective in appropriately controlled clinical trials. The work presented in this issue of the Annals of Surgery exemplifies recent advances

in this field. Significant progress has been made, but important hurdles need to be overcome before support of the acutely failing liver becomes a clinical reality.

Achilles A. Demetriou, MD, PhD

References

Tandon BN, Gandhi BM, Joshi YK, Irshad M, Gupta H. Hepatitis virus non-A, non-B: the cause of major public health problem in India. Bull WHO 1985; 63: 931- 934.