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SPECIAL ARTICLE

Liver Dialysis: A Review

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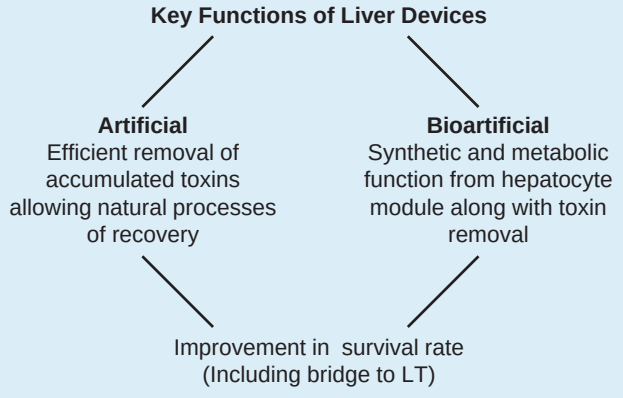
INTRODUCTION

Liver dialysis, like kidney dialysis for end-stage kidney disease, refers to the use of extracorporeal devices for temporary support when the liver fails. Unlike the toxemia of kidney failure, the toxins that are retained in the blood when the function of the liver becomes severely deranged, including many protein bound as well as water soluble toxins. These include small molecular weight toxins (ammonia, phenol, false neurotransmitters, free bile acids, etc.) also mediators of inflammation (e.g. cytokines, chemokines) vasoactive substances, cell growth inhibitors (e.g. TGFβ1) and endotoxin.[1] Their exact role in causing neurological and other organ impairment and in aggravating injury to the liver, remains undetermined.

The beneficial effects, clinically, of clearing the blood of such toxins were shown very early in the history of temporary liver support when exchange transfusion was tried in patients with fulminant hepatic failure and shown to be followed by temporary improvements in encephalopathy. A similar application was returned 10 years later with the use of plasma exchange.[2] This approach was taken further in 1994, by Fin Larsen of the Copenhagen Liver Unit. The technique that he developed was of high volume plasmapheresis where 16% of the body weight is exchanged with FFP daily.[3] The controlled clinical trial that he set up in patients with acute liver failure (ALF) closed in 2009, with 182 patients entered. According to a personal communication from him, around 20% survival benefit was in the group of patients who were not transplanted.

The two pathways of development in liver support devices, namely artificial and bioartificial, are based on different premises (Box 1). Whether there is a need to provide supplementary metabolic and synthetic functions in addition to efficient removal of toxic substances in improving survival, is of fundamental importance. The findings to date with respect to the provision of greater synthetic and metabolic function are, in the writer's opinion, unconvincing. This is possibly because many of the cell lines are used in the biological modules whether porcine, primary human, tumor cell subclones or immortalized human hepatocyte preparations have limitations in terms of functional capacity. The first major controlled clinical trial of a bioartificial device which was carried out by Demetriou, a pioneer in this field, gave disappointing results in patients with fulminant hepatic failure or primary graft failure without a statistically significant improvement in overall survival (Box 2). The study also illustrated the profound impact of transplantation on survival in ALF, which makes analysis of a possible beneficial effect from the device extraordinarily difficult.[4] More encouraging results with respect to survival were reported in a recently conducted trial of extracorporeal liver assist device (ELAD™) based on a tumor cell clone which has been greatly improved over the years.[5] This was carried out in China (Box 3) and led the manufacturers – Vital Therapies Inc, San Diego Ca, to set up a multicenter controlled clinical trial initially in the USA. Early findings from this (Box 4), on the safety and efficacy of the device were reported at

Box 1



Box 2

Randomized, multicenter, controlled clinical trial of BAL (Porcine cells) in ALF[4]

- 147 cases stage III-IV Enceph and 24 PNF. Treatment for 6 hours daily
- 30 days survival—71% Bioartificial livers (BAL), 62% standard care
- Profound impact of transplantation (in 54%) on survival—84% *vs* 46% not transplanted.

Allowing for compounding factors, survival fulminant groups significantly higher (p = 0.048)

Box 3

Interim results of randomized controlled trial of ELAD™ in acute-on-chronic liver disease[5]

90 patients at two Chinese centers; chronic HBV or HCV with episode of acute decompensation

- Continuous ELAD perfusion for 43-119 hours. Thirty days transplant free survival, 86% *vs* 47% in controls (p = 0.004)

Biochemical improvement 'supported increased survival'
Platelet ↓ 28% managed by transfusion

Box 4

Safety and efficacy of ELAD in AoCLF[6]

SOFA score ≥ 9, MELD ≥ 32 or 24 if grade III/IV HE or HRS randomized: 2:1—(14 ELAD + SMT, 4 SMT), continuous perfusion

- At 30 days more patients achieved trial from support (TFS) in ELAD
- Overall survivals similar—46% *vs* 50%

Ongoing multicenter trial—perfusions for 3-6 days, end points include progression free duration

Box 5

Albumin dialysis (MARS) in cirrhosis and advanced encephalopathy: A prospective, controlled randomized multicenter trial[7]

Daily dialysis of 6 hours for up to 5 consecutive days compared with standard treatment

- Two grade improvement in HE (4 → 2 or 3 → 1) reached significantly faster and more frequently in MARS group
- Accompanied by significant decrease in ammonia, bilirubin bile acids, creatinine and aromatic amino acids

Box 6

MARS in AoCLF – Relief study[8]

189 patients from 19 centers across 10 countries: Alcohol 94% (abuse 77.6%). Infection triggering factor in 30.6%. 10 sessions 6-8 hours/21 days

- 28 day survival—58.2% *vs* 60%
- Significant decrease in serum creatinine and bilirubin, higher improvement in HE and less worsening of liver failure (< 0.04)
- Number of MARS sessions—6.5 (SD 3.1)

this year's European association for the study of the liver (EASL) meeting in Vienna.[6]

The concept of albumin dialysis and the development of the device known as molecular adsorbent recycling system (MARS) by Stanger and Mitzner from the University of Rostock between 1993 and 1997, marked a major step forward. Using an albumin impregnated membrane with a pore size of 50 kDa, significant removal of a range of protein bound toxins has been demonstrated *in vitro* and *in vivo*. As I understand it, more than 9,000 patients from 45 countries have now been treated worldwide with the device. Clinical studies have shown improvement in the pathophysiological manifestations of liver failure, including encephalopathy, circulatory dysfunction and renal impairment, in parallel with reductions in measured toxemia. In the carefully controlled clinical trial of the device in cirrhotic patients with advanced encephalopathy carried out in the USA (Box 5), a statistically significant improvement in encephalopathy was demonstrated.[7] The anticipation was that such improvements in clinical manifestations and in biochemical abnormalities would translate through to improvements in overall survival. However, this was not found in the recently completed controlled clinical trial of MARS carried out in acute-on-chronic liver failure (AoCLF)—the relief study. An initial analysis of the results (Box 6), in a study of 189 patients was presented at this year's EASL meeting.[8] Another recent controlled clinical trial of MARS, this time in ALF and carried out in France, showed the difference in survival between the MARS treated and controls to be very close to statistical significance for the paracetamol etiology group where one would anticipate the greatest potential for spontaneous recovery.[9]

The other artificial device currently under trial at the present time is known as Prometheus. In contrast to MARS, it is based on albumin-permeable membrane with a pore size of 300 kDa. The separated plasma fraction is cleared of protein bound toxins by passage through columns of adsorbents. Before being returned to the patient, the plasma is also passed through a standard dialysis membrane to eliminate water soluble toxins. A comparison study with MARS showed a better reduction in bilirubin level, particularly of the unconjugated fraction, although attenuation of the characteristic hyperdynamic circulation of liver failure was found only with MARS in association with decreased levels of vasoactive substances, including plasma renin activity and nitric oxide.[10] The results of the controlled clinical trial of this device in AoCLF (Helios study) were also reported at the EASL meeting in Vienna (Box 7). As with the relief study, no statistically significant difference in overall survival was demonstrated, though there was a survival advantage in those with the hepato-renal syndrome and in those with a high MELD score.[11]

Box 7

Prometheus in AoCLF—Helios study[11]

145 patients from 10 centers across seven countries. 56% chronic alcohol abuse, MELD 27 ± 10, 8-11 treatments of 4 hours minimum first 3 weeks

- 28 days survival—66% *vs* 63% including 28 patients transplanted
- In predefined subgroups significant survival advantage for HRS type I (p < 0.04) and MELD score > 30 (p < 0.02)

Possible explanations for why overall survival is not increased despite improvements in various components of the AoCLF syndrome include inadequacy of the perfusion regime, either from insufficient duration or number of treatments. Another possibility relates to the case mix of the patient group with inclusion of cases without the potential for recovery. Failure to completely control certain important components of the syndrome of AoCLF, particularly infection is a further explanation. Here, the removal of released endotoxin into the plasma may be critical.

CONCLUSION

There has been considerable progress in the development of safety of extracorporeal forms of temporary liver support and of efficacy particularly of the artificial devices. Continuing research into their design and function is needed, and also there needs to be more research done into the mechanisms of liver regeneration and recovery processes in both AoCLF and in ALF, if liver dialysis is to satisfy requirements and achieve an enduring place in the treatment of end-stage liver disease.

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