Running Title: Update on Extracorporeal Liver Support

Authors

Dev Katarey, Rajiv Jalan

Affiliations

Liver Failure Group, UCL Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom

Correspondence:

Rajiv Jalan, Liver Failure Group, UCL Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, Pond Street, London, United Kingdom, NW3 2QG. E-mail: r.jalan@ucl.ac.uk. Phone: 01144 2077 940500.

Conflict of Interest:

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Ltd, a spin out company from University College London. He is also a Founder of Thoeris Ltd.

Abstract

Purpose of review: Extracorporeal liver support (ELS) is a large unmet need in day-to-day hepatology practice. In an era of ever-improving outcomes with liver transplantation for very sick patients with either acute liver failure or acute-on-chronic liver failure, the outcomes for similar patients who are ineligible for transplantation remains poor. Providing a bridge to recovery from these catastrophic conditions is the aim of ELS, and we aim to review the evidence to date of different ELS devices as well as look to the future of ELS device development.

Recent findings: Studies on different ELS devices shave been relatively consistent in their inability to demonstrate a survival benefit, however recent published evidence has suggested ways in which the three key pillars to ELS – the disease (patient selection), device (ELS system), and dose (intensity) – may be modified in order to attain a more positive outcome. New devices are grasping these concepts and demonstrating encouraging pre-clinical results.

Summary: ELS devices to studied to date have not been able to significantly improve transplant-free survival. Newer ELS devices are currently in clinical trials and their results are awaited.

Keywords: extracorporeal liver support, dialysis

Introduction

The potential of the liver to regenerate and return to normality even in patients with advanced liver failure provides the rationale to develop extracorporeal liver support (ELS) techniques that may be used to keep the patient alive and provide an improved environment for regeneration. As the name implies, ELS devices work outside the body where patient's whole blood or plasma is passed through an adsorption, dialysis or cellular filter to remove circulating toxins and/or provide functional substances to the patient. The potential for reversibility clearly exists in patients with both acute liver failure (ALF) and also acute-on-chronic liver failure (ACLF) where recovery from an episode of liver failure can be associated with long term survival [1, 2]. Therefore, ELS may be indicated in patients to improve their transplant-free survival. Alternatively, ELS may be indicated in liver failure patients as a bridge to liver transplantation with the aim of stabilising them until such time as a liver for transplantation becomes available. Other potential uses of ELS may be to treat a complication such as hepatic encephalopathy, severe pruritus, overwhelming infection or renal dysfunction.

Types of Extracorporeal Liver Support and Results from Clinical Trials

There are two main types of ELS: those that are purely detoxification devices ('artificial devices'), and those that incorporate hepatocytes into the device to provide functional biological activity that may fulfil some of the detoxification and synthetic needs of the patient ('biological devices'). The best studied artificial ELS devices are based on the principles of albumin dialysis and plasma exchange, and the extracorporeal liver assist device is the best studied biological ELS device. The following section will focus on the results from the major studies using these devices (Table 1).

Artificial ELS

Albumin Dialysis

Albumin dialysis is based on the concept that albumin has pleiotropic functions and is more than a plasma volume expander. It provides many biological functions including most of the thiol function of

plasma and has important binding sites that becomes dysfunctional in liver failure. As a result, the ability of albumin to bind circulating toxins is dramatically reduced resulting in their accumulation and subsequent organ dysfunction [3-5]. Extracorporeal albumin dialysis attempts to remove this toxin burden providing an opportunity for the liver to recover.

Molecular adsorbent recirculating system

The molecular adsorbent recirculating system (MARS; Gambro, Sweden) is the best studied ELS device, first described in 1993. Blood is circulated across an albumin-impermeable 50-60kDa cut-off membrane against a 20% human albumin solution dialysate [6-8]. MARS has been investigated in patients with ALF and ACLF.

In ALF, clinical trials consistently demonstrate a lack of survival benefit [9-11]. The best of these studies, the FULMAR study, was a French multi-centre randomized controlled trial which compared MARS + standard medical therapy (SMT) (n=57) versus SMT alone (n=53) in ALF patients. There were no differences in 6-month survival between the groups on a modified intention-to-treat analysis (75.5% vs. 82.9%, P=0.50) [11].

In patients with ACLF, MARS has been shown to have many positive effects on individual organ function. Beneficial effects have been observed in the severity of portal hypertension [12, 13], hepatic encephalopathy (HE) [14], renal function [6] and pruritus [15]. The largest controlled clinical trial of MARS in ACLF patients is the RELIEF study which randomized patients to either MARS+SMT (n=95) or SMT (n=94). In this study, MARS was able to demonstrate a significant reduction in serum creatinine, bilirubin, and HE grade compared with SMT. However, the primary outcome of 28-day survival was indifferent on the intention-to-treat analysis (60.7% vs. 58.9%, P=0.79) [16]. In a recent meta-analysis using individual patient data, improved 10- and 30-day survival was demonstrated with high intensity therapy of five sessions or more in the total cohort (10-day survival 98.6% vs. 82.8%, P=0.001; 30-day

survival 73.9% vs. 64.3%, P=0.032) and in the ACLF subgroup (10-day survival 97.8% vs. 78.6%, P=0.001; 30-day survival 73.3% vs. 58.5%, P=0.041) [17*].

Prometheus

The Fractionated Plasma Separation and Adsorption (FPSA) device, also known as Prometheus (Fresenius Medical Care, Germany), is another albumin-based ELS device which separates albumin/plasma from blood by fluxing whole blood across a larger 250-300kDa cut-off membrane into a secondary circuit which contains two filters. These filters are designed to improve albumin function and adsorb toxins in order to improve the functional status of the patient [18, 19]. The HELIOS study, a large randomized controlled trial, compared Prometheus+SMT (8-11 rounds, at least 4 hours each) (n=77) or SMT alone (n=68) in ACLF patients. A sustained reduction in bilirubin was observed with Prometheus therapy at 28 days, however no differences were seen in 28-day survival (66% vs. 63%, P=0.70) or 90-day survival (47% vs. 38%, P=0.35) on an intention-to-treat analysis. On subgroup analysis, however, those with a Model for End-Stage Liver Disease (MELD) score >30 did demonstrate a 90-day survival benefit with Prometheus therapy versus SMT alone (log-rank P=0.0241) [20]. Although other studies had reported improved creatinine and ammonia with Prometheus therapy versus SMT [21, 22], this was not confirmed in the HELIOS study [20]. Like MARS, the results to date cannot warrant recommendation for using Prometheus to treat patients outside of a trial setting.

<u>Plasma Exchange</u>

High-volume plasma exchange (HVP), described extensively for many other medical indications, has also been investigated as an ELS device. HVP relies on plasma separation and elimination from whole blood. The subsequent replacement of lost fluid and blood products is most commonly achieved with fresh frozen plasma, but human albumin solution can also be used either in tandem or alone. Two large clinical trials have been conducted using HVP. Firstly, in ACLF, *Qin et. al.* (2014) report on their randomization of transplant-ineligible patients to either HVP+SMT (n=104) or SMT alone (n=130). They

reported a significantly improved 90-day survival (60% vs. 47%, P<0.05) and median survival (879 vs. 649 days, log-rank P<0.05). Although encouraging, this trial was done in a strict hepatitis B virus (HBV) cohort which limits the general applicability [23]. In ALF patients, *Larsen et. al.* (2015) reported on their randomized, multi-centre trial comparing HVP+SMT (n=92) versus SMT alone (n=90). Although survival was not different in either group when treatment was followed by transplantation, transplant-free survival to hospital discharge was significantly improved in those treated with HVP (58.7% vs. 47.8%; HR 0.56, 95% CI 0.36-0.86; P=0.0083). Furthermore, systemic inflammatory response syndrome (SIRS) and sequential organ failure assessment (SOFA) scores reduced significantly in the HVP group [24]. Although the benefits observed are slim, there is relatively homogenous evidence in well conducted trials to recommend HVP for transplant-ineligible patients.

Biological ELS

The extracorporeal liver assist device (ELAD; Vital Therapies, USA) differs from the aforementioned devices as ELAD utilises a biological dialyser. The hollow-fiber dialysis cartridges contain human hepatoblastoma (HepG2/C3A) cells which are able to survive the 3-10 day treatment regimen and mimic *in vivo* functions such as albumin synthesis and cytochrome P450 activity. Notably, they are less biologically active than primary hepatocytes with poor detoxification of ammonia [25, 26]. The most impactful study on ELAD was a phase III multinational, randomized, controlled trial comparing ELAD+SMT (n=96) with SMT alone (n=107) in patients with severe alcoholic hepatitis. No difference was seen in overall survival at any time points (51% vs. 49.5%, log-rank P=0.90), and following this result the development of ELAD was halted [27].

Overall, ELS devices to date have shown a marginal benefit at best in overall or transplant-free survival. There is still a wide gap in the market for such a device which can benefit patients with ALF and ACLF who represent the most profoundly unwell patients in hepatology.

Potential reasons for failure of ELS to improve survival and potential new solutions

The existence of these large clinical trials allows a detailed assessment of factors that may have contributed to the limited survival benefit of the various ELS systems in patients with both ALF and ACLF. The following sections will describe treating these critically unwell patients with ALF or ACLF with an ELS device that requires careful optimisation of three fundamental pillars: disease, device and dose of therapy.

The Disease

Acute Liver Failure

Over the past twenty to thirty years, the natural history of ALF has changed with far fewer deaths of patients on the waiting list and also the deaths of patients from cerebral edema has gone down considerably [28]. The failure of the FULMAR study to show a survival benefit is most likely because of the rapidity of obtaining an organ for liver transplantation (median time from randomization to liver transplantation of 16.2 hours [IQR 11.4-28.2 hours]) such that the median number of MARS therapy sessions was only one (IQR 0-7 sessions) [11]. Therefore, for an intervention such as MARS to have a chance to reduce mortality, the studies need to be performed in ALF patients that fulfil poor prognostic criteria but are not candidates for liver transplantation. Alternatively, studies should be performed in countries such as India or China where either access to liver transplantation is limited, or in countries such as the US where patients often wait for up to 5-7 days to receive a suitable organ [29, 30].

Acute-on-Chronic Liver Failure

ACLF, in contrast to ALF, was a poorly defined entity at the time when the RELIEF or HELIOS studies were performed and therefore both these studies most likely included patients with 'ACLF' whose mortality risk varied widely from 0-100%. On the other hand, patient selection for the ELAD trial comprised a large number that according to the ACLF diagnostic criteria would not be classed as having

the condition and therefore have a substantially lower risk of death. It was therefore not surprising that the very low mortality in the control group did not allow accurate determination of whether ELAD truly failed to improve survival [27]. The data from the CANONIC study clearly shows that the risk of mortality of patients with ACLF can vary from 0-100% based on their Chronic Liver Failure Consortium ACLF (CLIF-C ACLF) score [31]. This allows for more accurate prediction of mortality when a patient is identified as having ACLF. Scores ≤34 confer a ~5% 28-day mortality whereas scores ≥65 confer a ≥80% 28-day mortality [31, 32]. It is therefore possible that previous studies on ELS devices may have failed in-part because their cohorts may have had patients "too well" (CLIF-C ACLF score ≤34) or "too sick" (CLIF-C ACLF score ≥65) to observe a true benefit. The target population with salvageable liver disease and subsequent organ failures may be those with CLIF-C ACLF scores between 34-65.

The Device

Albumin Dialysis

The fundamental principle behind MARS and Prometheus assumed that the function of native albumin in the patient could be restored by the removal of toxins. This hypothesis is only partly true because subsequent investigations clearly showed that the function of the circulating albumin was reduced to about 15% of the healthy individual and could not be rejuvenated despite MARS therapy. This was because a proportion of the circulating albumin was irreversibly damaged [4]. Also, more recent studies have clearly shown that this damaged albumin in patients with ACLF is not only dysfunctional but also induces an inflammatory response [5]. Therefore, the damaged albumin needs to be removed and replaced. Also, many lines of investigation suggest that immune failure, which is a feature of ACLF that increases the risk of sepsis and mortality, is contributed to by circulating factors such as damage- and pathogen-associated molecular patterns (DAMPs, PAMPs) and their removal may improve immune function [33, 34]. Therefore, DIALIVE (Yaqrit/University College London, UK), a new artificial ELS, was conceived which incorporates two filters in series (Table 2). Utilising an artificial 60kDa high cut-off membrane, DIALIVE induces albumin loss which is then subsequently replaced via infusion of

human albumin solution [35]. Adding to this, the high cut-off membrane will also physically remove pro- and anti-inflammatory cytokines which may restore balance in the severe immune dysregulation seen in these cohorts [36]. The second membrane is a heparin-coated adsorption column that efficiently removes DAMPs and PAMPs. In pig models of paracetamol-induced ALF, DIALIVE has demonstrated improved survival, cardiovascular and respiratory function, and a reduction in endotoxemia compared with similar pigs treated with a sham device [35]. Currently, DIALIVE has finished recruiting for a first-in-human multi-centre, randomized, open-label, controlled trial [37].

Biological ELS

One of the problems with ELAD was the use of C3A cells, which is a cancer cell line, in the cartridge. Although this cell can be produced readily, it has the shortcoming of having a limited functional capacity [25, 26]. In order to improve on this, the spheroid reservoir bioartificial liver (SRBAL; Mayo Clinic; USA) has been developed which utilises primary pig hepatocytes (Table 2). This ELS device employs a hollow-fiber dialyser, akin to that in ELAD, to aid in detoxification of blood. In addition, the blood circuit passes through a bioreactor containing primary pig hepatocyte spheroids with the intent of further detoxification as well as applying synthetic liver function [38]. Primary hepatocytes are able to cluster into spheroids by stimulating them with an oscillatory frequency of 0.25Hz [39, 40]. To date, SRBAL has demonstrated encouraging pre-clinical data. In porcine D-galactosamine-induced ALF models, SRBAL was able to demonstrate superior survival, ammonia detoxification, and reduction in intracranial pressure compared with SBRAL without primary hepatocytes and SMT alone [38]. These findings were subsequently confirmed in 85% hepatectomy pigs randomized to the same treatment groups, and in addition, liver regeneration was also accelerated in the SRBAL group [41*]. First-in-human trials are being planned but have not yet started.

Dose of therapy

The data from the CANONIC study highlights important issues that should be considered in defining the duration of therapy for patients with ACLF. From the available data, it is clear that the first week of hospitalisation is pivotal in determining the outcome of patients with ACLF and their ACLF grade at day 3-7 from admission can predict 28-day and 3-month mortality [31]. These data are also confirmed by the meta-analysis of individual patients that show improved survival in those given high intensity treatment, described earlier [17*]. The second aspect that emerged from the CANONIC study was that the 3-month mortality of patients with ACLF grade 1 and 2 was almost twice that at 28-days implying that patients continue to die even after they recover from the initial episode of ACLF [31]. This suggests that ACLF patients that recover need to be followed up closely in the community and offered repeat ELS therapy if they develop ACLF again.

Conclusion

Although ELS devices to date have only shown marginal benefits in large clinical trials, these trials should not be considered failures. The numerous studies on the different artificial and biological ELS devices have provided the stepping-stones needed to better understand the three key pillars to successful ELS: disease, device, and dose of therapy. The aim of improving transplant-free survival in ALF and ACLF patients using ELS devices will further be shaped by the results from the DIALIVE and SRBAL clinical trials, and it should bring us closer to an answer for this large unmet need in hepatology clinical practice.

Key Points

1. Extracorporeal liver support has been predominantly investigated in acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) patients with a view to improve transplant-free survival.

2. Albumin-bases ELS devices, namely the molecular adsorbent recirculating system (MARS) and Prometheus, have not demonstrated any improvement in survival in studies conducted to date.

3. High-volume plasma exchange appears to improve short-term transplant-free survival in ALF patients.

4. The extracorporeal liver assist device (ELAD) did not demonstrate any survival benefit in a large phase III trial.

5. Newer ELS devices, namely DIALIVE and the spheroid reservoir bioartificial liver (SRBAL), have demonstrated encouraging pre-clinical results in pig models and clinical trials are either already underway or being planned.

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This meta-analysis has helped determine the minimum number of ELS therapy sessions required to provide a benefit with MARS and may guide future trial protocols.

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An important pre-clinical study demonstrating the efficacy of SRBAL in posthepatectomy pig models.

Dialysis Membrane	**Mechanism**	**Name**	**Multicenter RCT**	**Patient Type**	**Number of Patients**	**Survival Outcome(s)**
Artificial	Albumin-based	MARS	FULMAR (2013)	ALF	Total = 110 MARS = 57 SMT = 53	6-month survival 75.5% vs. 82.9%, P=0.50
			RELIEF (2013)	ACLF	Total = 189 MARS = 95 SMT = 94	28-day survival 60.7% vs. 58.9%, P=0.79
		Prometheus	HELIOS (2012)	ACLF	Total = 145 Prometheus = 77 SMT = 68	28-day survival 66% vs. 63%, P=0.70
	HVP	-	*Larsen et. al.* (2016)	ALF	Total = 183 HVP = 92 SMT = 91	Survival to hospital discharge higher with HVP (58.7% vs. 47.8%, HR 0.56, 95% CI 0.36-0.86, P=0.0083)
Biological	HepG2/C3A cells within dialysis cartridges	ELAD	*Thompson et. al.* (2018)	Severe alcoholic hepatitis	Total = 203 ELAD = 96 SMT = 107	28-day, 91-day and 5-year survival not significantly different

Table 1: Currently available ELS devices and the most prominent multicenter randomized controlled trials (RCTs) in which they were evaluated. MARS = molecular adsorbents recirculating system. HVP = high-volume plasma exchange. ELAD = extracorporeal liver assist device. ALF = acute liver failure. ACLF = acute-on-chronic liver failure. SMT = standard medical therapy. HR = hazard ratio. CI = confidence interval.

Dialysis Membrane	Mechanism	Name	Study	Model	Outcomes
Artificial	Albumin-exchange	DIALIVE	*Lee et. al.* (2015)	Pigs with paracetamol-induced ALF DIALIVE vs. Sham	Significantly improved survival, cardiovascular and respiratory function, reduction in endotoxemia in DIALIVE-treated pigs
Biological	Primary pig hepatocytes within a bioreactor	SRBAL	*Glorioso et. al.* (2015)	Pigs with D-galactosamine-induced ALF SRBAL vs. non-cellular SRBAL vs. SMT	Significantly improved survival and ammonia detoxification in SRBAL-treated pigs (versus non-cellular SRBAL and SMT, independently)

Table 2: ELS devices undergoing clinical trials at present. SRBAL = Spheroid reservoir bioartificial liver. ALF = acute liver failure. SMT = standard medical therapy.