

Review

Bench-to-bedside review: Current evidence for extracorporeal albumin dialysis systems in liver failure

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Abstract

Acute liver failure (ALF) and acute on chronic liver failure (AoCLF) carry a high mortality. The rationale for extracorporeal systems is to provide an environment facilitating recovery or a window of opportunity for liver transplantation. Recent technologies have used albumin as a scavenging molecule. Two different albumin dialysis systems have been developed using this principle: MARS (Molecular Adsorbent Recirculation System) and SPAD (Single-Pass Albumin Dialysis). A third system, Prometheus (Fractionated Plasma Separation and Adsorption), differs from the others in that the patient's albumin is separated across a membrane and then is run over adsorptive columns. Although several trials have been published (particularly with MARS), currently there is a lack of controlled studies with homogenous patient populations. Many studies have combined patients with ALF and AoCLF. Others have included patients with different etiologies. Although MARS and Prometheus have shown biochemical improvements in AoCLF and ALF, additional studies are required to show conclusive benefit in short- and long-term survival. The appropriate comparator is standard medical therapy rather than head-to-head comparisons of different forms of albumin dialysis.

Introduction

Acute liver failure (ALF) and acute on chronic liver failure (AoCLF) have a high mortality. ALF is defined as development of severe acute liver injury with impaired hepatic synthetic function and encephalopathy in a patient without previous liver disease [1]. AoCLF is defined as acute deterioration in liver function over a 2- to 4-week period in a patient with pre-existing chronic liver disease. In both conditions, the lack of the metabolic and regulatory function of the liver results in life-threatening complications that may include bleeding, renal

failure, hepatic encephalopathy (HE) or cerebral edema, cardiovascular failure, and susceptibility to infections culminating in multi-organ failure [2].

Currently, the only effective therapy for patients with liver failure is liver transplantation. Many patients die, however, before a suitable graft is available, and for those who progress to multi-organ failure, transplantation is not an option. The liver often maintains some regenerative capacity, so the rationale for supportive therapy and extracorporeal systems is to provide an environment facilitating recovery to create or prolong a window of opportunity for liver transplantation or, in the best-case scenario, until native liver recovery occurs in ALF or a period of stability for those with AoCLF [3].

In liver failure, a variety of 'toxins' accumulate as a result of impaired hepatic function and clearance. Ammonia, inflammatory cytokines, aromatic amino acids, and endogenous benzodiazepines have been implicated in the development of HE and cerebral edema. Other systemic factors such as nitric oxide and cytokines have been linked with circulatory and renal dysfunction in liver failure. Pro-inflammatory cytokines and oxidative stress have broad effects ranging from increased capillary permeability to modulating cell-death and immune dysregulation.

Various forms of dialysis were used in the treatment of liver failure in the 1970s but failed to show benefit, possibly because the majority of toxins in liver failure are water-insoluble and albumin-bound and are poorly cleared by

ALF = acute liver failure; AoCLF = acute on chronic liver failure; CBF = cerebral blood flow; CVVHD = continuous venovenous hemodialysis; FPSA = fractionated plasma separation and adsorption; HBV = hepatitis B virus; HE = hepatic encephalopathy; HRS = hepatorenal syndrome; IL = interleukin; MAP = mean arterial pressure; MARS = Molecular Adsorbent Recirculation System; SMT = standard medical therapy; SOFA = Sequential Organ Failure Assessment; SPAD = Single-Pass Albumin Dialysis; SVRI = systemic vascular resistance index; TNF- α = tumor necrosis factor- α .

Table 1

Molecular Adsorbent Recirculation System in acute on chronic liver failure

Study	Number	Controlled	Improvements			Survival (30 days) ^a
			Biochemical	CVS	CNS	
Stange <i>et al.</i> [7]	13	No	Yes	N/A	Yes	69%
Schmidt <i>et al.</i> [10]	8	No	Yes	Yes	No	50%
Jalan <i>et al.</i> [37]	8	No	Yes	Yes	Yes	50%
Di Campi <i>et al.</i> [38]	13	No	Yes	N/A	Yes	38%
Mitzner <i>et al.</i> [8]	13	Yes	Yes	Yes	No	Yes (37.5% versus 0% at 7 days)
Heemann <i>et al.</i> [9]	23	Yes	Yes	Yes	Yes	Yes (90% versus 55%)
Sen <i>et al.</i> [11]	18	Yes	Yes ^b	No	Yes	No (45% in both)
Blei [16]	70	Yes	N/A	N/A	Yes	N/A
Laleman <i>et al.</i> [12]	18	Yes	Yes ^c	Yes	N/A	N/A

Biochemical improvements: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia. ^aPercentages indicate uncontrolled survival data; ^btrend did not reach statistical significance; ^cbilirubin and bile acids only. CNS, improvement in hemodynamic parameters (mean arterial pressure, heart rate, vasopressor requirements); CNS, decrease in hepatic encephalopathy grade (neurological improvement); N/A, not assessed.

conventional hemodialysis or hemofiltration systems [4]. Charcoal hemoperfusion was similarly ineffective in a controlled study, possibly in part due to biocompatibility issues [5].

Albumin administration has been shown to be beneficial in spontaneous bacterial peritonitis and hepatorenal syndrome (HRS) partly due to its ability to bind toxins [4]. Recent artificial liver support technologies have used albumin as a binding and scavenging molecule. Albumin dialysis involves dialyzing blood against an albumin-containing solution across a highly permeable high-flux membrane. The blood-bound toxins are cleared by diffusion and taken up by the binding sites of the albumin dialysate. Two different albumin dialysis systems have been developed using this principle: MARS (Molecular Adsorbent Recirculation System) and SPAD (Single-Pass Albumin Dialysis). Prometheus (Fractionated Plasma Separation and Adsorption, or FPSA) differs from the others in that the patient's plasma is separated across a membrane and then is run over adsorptive columns. In this review, we will examine the current evidence for the use of these three technologies in patients with liver failure and its complications.

Materials and methods

Relevant articles were found by electronic literature search from the National Institutes of Health (PubMed) database as well as bibliographies of recovered articles. We included full-length articles written in English between 1999 and 2006. Articles were excluded if statistical comparisons (*p* values) were not provided versus baseline in uncontrolled studies or versus the control group in randomized studies. In the absence of randomized studies, our comments reflect a narrative review of the available literature.

Results

I. Molecular Adsorbents Recirculation System

MARS was originally developed by Stange and colleagues [6] (Teraklin AG, Rostock, Germany) in 1993. The system consists of a blood circuit, an albumin circuit, and a classic 'renal' circuit. Blood is dialysed across an albumin-impregnated high-flux dialysis membrane; 600 ml of 20% human albumin in the albumin circuit acts as the dialysate. Albumin-bound toxins in blood are released to the membrane. These are subsequently picked up by albumin in the dialysate, which then undergoes hemodialysis/hemofiltration if required. The albumin dialysate is subsequently cleansed via passage across two sequential adsorbent columns containing activated charcoal and anion exchange resin. These columns remove most of the water-soluble and albumin-bound toxins. Because of the pore size of the membrane, substances with a molecular weight of more than 50 kDa, such as essential hormones and growth factors bound to albumin, are not removed [7].

Although there is a large amount of uncontrolled data about MARS use, only a few small controlled studies to date have examined the utility and safety of MARS in patients with complications of liver failure. Most have focused on improvements in biochemical profile, HE, and HRS. The benefit of MARS has been more clearly shown in patients with AoCLF (Table 1).

Molecular Adsorbent Recirculation System and acute on chronic liver failure

In 2000, Mitzner and colleagues [8] reported 13 patients with AoCLF and type 1 HRS treated with MARS. Patients received a mean of five treatments and did not receive vaso-

pressors nor were any transplanted. The authors showed a 37.5% absolute survival benefit at day 7 versus 0% in controls. Significant decreases in creatinine and bilirubin were also noted in the MARS group.

Subsequently, Heemann and colleagues [9] randomly assigned 23 patients with AoCLF (19 were alcoholics) to MARS or standard medical therapy [SMT] (including dialysis if necessary). Inclusion criteria included bilirubin of greater than 340 $\mu\text{mol/l}$, HE of greater than grade 2, and renal dysfunction. Patients in the MARS group received up to 10 treatments in the first 2 weeks. At day 30, 11/12 patients in the MARS group were still alive, compared to only 6/11 in the control group ($p < 0.05$). There were also statistically significant decreases in bilirubin (43%) and bile acids (29%) in the MARS group but not in the control group. A statistically significant increase in mean arterial pressure (MAP) ($p < 0.05$) as well as reductions in creatinine and HE grade ($p < 0.06$) were noted in the MARS group. Although improvements with MARS were significant compared to baseline, it is difficult to extrapolate these results beyond 30 days. This study was predominantly composed of patients with alcoholic cirrhosis with a superimposed acute injury related to either recent drinking or infection. Therefore, these results may not be applicable to other populations with different etiologies of cirrhosis.

Molecular Adsorbent Recirculation System and hemodynamics in acute on chronic liver failure

Although early uncontrolled studies have shown improvement in MAP in patients with AoCLF on MARS, results have been mixed in larger trials. In 2001, Schmidt and colleagues [10] reported an uncontrolled study of eight patients with AoCLF who received a single 10-hour MARS treatment. Statistically significant increases over baseline in MAP and systemic vascular resistance index (SVRI) (both $p < 0.05$) were noted. However, Sen and colleagues [11] were unable to reproduce these findings in their trial of 18 patients with alcohol-related AoCLF randomly assigned to receive MARS or SMT (including hemodialysis if indicated) over 7 days. This study also assessed the effect of MARS on cytokine profiles and nitric oxide, a potent vasodilator thought to have a significant effect on systemic vascular resistance in liver failure. Although HE improved significantly in the MARS group compared to control ($p < 0.05$), there were no statistically significant differences in cytokines, ammonia, malondialdehyde (marker of oxidative stress), or nitric oxide levels. There also was no statistically significant difference in MAP noted in either group from baseline nor mortality benefit at 30 days (4/9 alive in each group). The study of Schmidt and colleagues [10] assessed hemodynamics after one run on MARS, whereas the results of Sen and colleagues [11] were obtained after multiple MARS treatments.

Interestingly, a more recent study of 18 patients with AoCLF (alcoholic hepatitis) compared the hemodynamic effects of MARS versus Prometheus versus SMT (six patients in each

arm; see next section) [12]. They showed statistically significant increases in MAP and SVRI and a decrease in endogenous vasoactive compounds with MARS compared to Prometheus and SMT. Clearly, larger randomized controlled trials are needed to resolve this issue.

Molecular Adsorbent Recirculation System and cerebral blood flow in acute on chronic liver failure

Raised intracranial pressure is a cause of death in patients with ALF. Although cerebral edema is rare in AoCLF, HE may result in significant morbidity with loss of airway protection, respiratory sepsis, and malnutrition. Accordingly, Schmidt and colleagues [13] assessed the effect of MARS on cerebral blood flow (CBF) in eight patients with AoCLF. Each patient received a single 10-hour MARS treatment. CBF was assessed by middle cerebral artery transcranial doppler imaging alone. This commonly used methodology has been previously validated using technetium-99 single-photon emission computed tomography in concert (not used in this study) [14]. In this cohort, CBF increased from baseline (mean velocity of 42 to 72 cm/s; $p < 0.05$). Clinically, the grade of clinical HE improved in three patients and remained unchanged in the other five. Significant decreases in bilirubin and arterial ammonia were also noted ($p < 0.05$). These results may reflect the ability of MARS to decrease intracerebral glutamine via reductions in ammonia [15]; however, studies to date have not assessed the effects of serial MARS treatments on CBF at more distant time endpoints.

MARS has demonstrated consistent benefit in HE in patients with AoCLF. Blei [16] randomly assigned 70 patients with grade 3 or 4 HE to MARS ($n = 39$) and SMT ($n = 31$). The need for ventilation and the use of sedation were equal in both groups. Patients in the MARS group received therapy for 6 hours daily for 5 days or until a 2-grade improvement in HE was achieved. At day 5, 72% of patients on MARS had achieved a 2-grade improvement in HE versus 45% in the SMT group ($p = 0.017$).

Molecular Adsorbent Recirculation System and acute liver failure

There are limited controlled data examining the effect of MARS in ALF (Table 2). In 2003, Schmidt and colleagues [17] conducted a study to assess the effects of a single 6-hour MARS treatment on hemodynamics, oxygen consumption, and biochemical profile in patients with ALF (HE grade 3/4 developed within 7 days of symptoms). They randomly assigned 13 patients with ALF due to acetaminophen ($n = 10$), hepatitis B virus (HBV) ($n = 2$), and disulfiram ($n = 1$). Eight received MARS therapy and five received SMT with cooling to match hypothermia induced by MARS. Oxygen consumption decreased by 22% ($p < 0.05$) in the MARS group, whereas there was no significant change in the control group. SVRI increased by 46% in the MARS group during the 6-hour run treatment versus a 6% increase in the controls ($p < 0.0001$). MAP also increased in the MARS

Table 2**Molecular Adsorbent Recirculation System in acute liver failure**

Study	Etiology	Number	Controlled	Improvements			Survival (30 days)
				Biochemical	CVS	CNS	
Novelli <i>et al.</i> [39]	Fulminant	9	No	Yes	N/A	Yes ^a	66%
Isoniemi <i>et al.</i> [40]	Toxic	26	No	Yes	N/A	N/A	88%
Tsai <i>et al.</i> [19]	Hepatitis B virus	10	No	Yes	Yes	Yes	30%
Lee <i>et al.</i> [20]	Drug (herb)	13	No	Yes	N/A	No	15%
Lai <i>et al.</i> [21]	Drug/Non-A non-B hepatitis	10	No	No	Yes ^b	No	30%
Camus <i>et al.</i> [41]	Mixed	23	No	Yes ^c	N/A	Yes	N/A
Schmidt <i>et al.</i> [17]	Hepatitis B virus/Acetaminophen	13	Yes	Yes ^c	Yes	N/A	No (62.5% versus 60%)
El Banayosi <i>et al.</i> [18]	Ischemia	27	Yes	No ^d	N/A	N/A	Yes (50% versus 32%)

Biochemical improvements: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia. ^aStatistics not provided; ^bstatistically significant after first but not second MARS treatment; ^conly bilirubin and creatinine were statistically significant; ^dnon-significant improvement in bilirubin. CNS, improvement in hemodynamic parameters (mean arterial pressure, heart rate, vasopressor requirements); CNS, decrease in hepatic encephalopathy grade (neurological improvement); N/A, not assessed.

group ($p < 0.001$), whereas pressure was unchanged in controls. Compared to baseline, there were significant reductions in bilirubin, creatinine, and urea ($p < 0.05$) but not in ammonia in the MARS group. Survival was no different between the MARS and control patients.

Other studies have shown biochemical improvements with MARS in ALF without significant mortality benefit. In a controlled study of 27 patients treated for ALF due to cardiogenic shock, El Banayosi and colleagues [18] demonstrated non-significant reductions in conjugated and total bilirubin and mortality (Table 2). However, it is unclear whether this population truly met criteria for ALF, as there is no mention of grade of HE. In a case series of 10 patients with ALF due to HBV, Tsai and colleagues [19] demonstrated biochemical reductions (Table 2) at 3 months but mortality was 70% with one patient receiving a liver transplant. Lee and colleagues [20] have reported similar outcomes with MARS in a series of 13 patients with drug-induced ALF: a statistically significant reduction in total bilirubin after a single MARS treatment ($p < 0.006$) but an overall mortality of 85% at 20 days.

Molecular Adsorbent Recirculation System and hemodynamics in acute liver failure

Lai and colleagues [21] reported 10 consecutive patients (paracetamol 8, non-A non-B hepatitis 1, and isoniazid 1) admitted with ALF and grade 3/4 HE who were treated with MARS for 8 hours on 2 consecutive days. During the first MARS treatment, there were significant increases in SVRI ($p = 0.02$) and cardiac index ($p = 0.01$). However, these changes were not maintained to the end of the second MARS session. No significant changes in MAP or intracranial pressure, as measured by reverse jugular bulb saturation, were noted. Bilirubin levels were not significantly decreased

after MARS therapy. Three patients (30%) survived; all had paracetamol hepatotoxicity and recovered without transplant.

Molecular Adsorbent Recirculation System and inflammatory profile

It has been suggested that MARS has a beneficial effect in patients with multi-organ dysfunction due to the inflammatory milieu present in liver failure. Guo and colleagues [22] reported an uncontrolled mixed cohort treated with MARS (not shown in Tables 1 and 2); 11 patients had ALF and 13 had AoCLF. Entry requirements included evidence of two or more of the following organ complications; HRS, HE (grade 2 or greater), disseminated intravascular coagulopathy, acute respiratory distress syndrome, variceal bleeding, sepsis, and cardiovascular failure. In total, the 24 patients received 66 treatments (6 to 24 hours per treatment) over the 7 days. Their results showed a statistically significant decrease in levels of nitric oxide, tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-8, and interferon-gamma ($p < 0.01$). Significant improvements were also noted in level of consciousness (Glasgow Coma Score of 7 to 13), renal function, respiratory function, as well as increase in MAP ($p < 0.01$ for all three comparisons). This study did not differentiate between ALF and AoCLF in subsequent analysis. The majority of patients had HBV (17/24).

Recently, Stadlbauer and colleagues [23] assessed cytokine levels in eight patients with AoCLF of diverse etiologies undergoing alternating treatments with MARS and Prometheus in a random crossover design. Thirty-four treatments (17 MARS and 17 Prometheus) were available for analysis. Although measurable plasma clearances were detected for IL-6, IL-8, IL-10, and TNF- α , none was significant for MARS or Prometheus. Based on these studies, MARS does not

Table 3**Prometheus in liver failure**

Study	Classification	Number	Controlled	Improvements			Survival
				Biochemical	CVS	CNS	
Rifai <i>et al.</i> [28]	Acute on chronic liver failure	11	No	Yes	No	No	28% at 30 days
Skwarek <i>et al.</i> [31]	Acute liver failure	13	No	Yes	N/A	N/A	23% at 6 months
Laleman <i>et al.</i> [12]	Acute on chronic liver failure (ethanol)	18	Yes	Yes ^a	No	N/A	N/A

Biochemical improvements: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia. ^aBilirubin and bile acids only. CNS, improvement in hemodynamic parameters (mean arterial pressure, heart rate, vasopressor requirements); CNS, decrease in hepatic encephalopathy grade (neurological improvement); N/A, not assessed.

appear to have a significant impact on the inflammatory profile in AoCLF.

Molecular Adsorbent Recirculation System and bleeding

Blood coagulation is the result of a complex interaction between procoagulant, anticoagulant, and fibrinolytic proteins, many of which are synthesized by the liver. As previous liver support/perfusion systems have been associated with significant bleeding rates, two studies have studied coagulation and bleeding with MARS. Faybik and colleagues [24] described 33 patients undergoing 61 MARS treatments (15 with ALF, 8 with AoCLF, 3 with liver graft dysfunction, 5 with sepsis, and 2 with cholestasis). Although there was a statistically significant decrease in platelets and fibrinogen, platelet function as measured by thromboelastography was unaffected. Three moderate bleeding complications occurred requiring transfusions (3 to 4 units of packed cells), but none of the MARS runs had to be discontinued.

A second study by Doria and colleagues [25] examined 9 patients with cirrhosis who underwent MARS therapy: 6 with AoCLF and 3 with intractable pruritis. Four patients developed bleeding while on MARS: 3 from gastrointestinal sources and 1 from a genitourinary source. Four patients who bled during MARS treatments subsequently died. MARS resulted in a minor but statistically significant reduction in platelet count (37 to 32 per millilitre; $p < 0.05$), worsened platelet function by thromboelastography ($p < 0.05$), and an increase in international normalised ratio for prothrombin time (1.9 to 3.5; $p =$ not significant).

Clearly, patients with all forms of liver failure are at high risk for bleeding complications with or without MARS treatments. Controlled trials are necessary before the magnitude of these risks can be quantitated.

II. Prometheus: Fractionated Plasma Separation and Adsorption

Prometheus (Fresenius AG, Hamburg, Germany), or FPSA, was introduced in 1999. Its physiological basis is different than MARS; patient plasma is fractionated through an

albumin-permeable filter with a cutoff of 250 kDa. Albumin and other plasma proteins cross the membrane and pass across two columns in series: one an anion-exchange column, another a neutral resin adsorber. The cleansed albumin/plasma is returned to the standard blood pool circuit where it is then treated by conventional high-flux hemodialysis.

Early *in vitro* data showed that Prometheus effectively cleared bilirubin, bile acids, and aromatic amino acids [26]. Important compounds with a molecular weight of more than 250 kDa, such as fibrinogen, were unchanged. A recent study showed that in 18 patients with AoCLF (9 MARS and 9 Prometheus), greater reduction ratios in total bilirubin, conjugated bilirubin, and bile acids were obtained with Prometheus therapy than with MARS treatments with identical duration of therapy (5 hours), blood, and dialysate flow [27].

To date, no large controlled studies on Prometheus have been published but some small case series have been reported (Table 3). In 2003, Rifai and colleagues [28] reported 11 patients with AoCLF, HE, and HRS who were treated on 2 consecutive days (more than 4 hours) with Prometheus. Statistically significant reductions in conjugated and unconjugated bilirubin, bile acids, and ammonia levels were noted. Despite the drop in ammonia levels, no clinical change in HE was noted. Eight of 11 patients died, including one due to variceal bleeding. Rifai and colleagues [29] have also reported Prometheus use in 10 patients with HRS who underwent two consecutive Prometheus treatments. Statistically significant decreases in creatinine and urea levels and improvement in arterial blood pH were observed. This is not unexpected since conventional dialysis is incorporated into the circuit. Significant decreases in serum-conjugated bilirubin, bile acids, and ammonia levels were also noted. In the same patient population (AoCLF), Rifai and colleagues [30] have also shown that after two treatments, Prometheus did not significantly alter inflammatory cytokine levels (C reactive protein, IL-6, and TNF- α).

Prometheus has also been used as a bridge to liver transplantation in patients with ALF. Skwarek and colleagues

[31] reported 13 patients with ALF who received a total of 35 treatments lasting 6 to 10 hours. They noted statistically significant decreases in total bilirubin and ammonia. Improvements noted in acid-base balance and MAP did not reach statistical significance. Seven patients were bridged to liver transplantation, but only 3 were alive at 6 months. In summary, Prometheus does not appear to improve mortality in ALF unless transplant is performed, and even then, mortality is high.

The effect of Prometheus on systemic hemodynamics has not yet been established. Laleman and colleagues [12] compared the hemodynamic effects of Prometheus with MARS in 18 patients with AoCLF secondary to severe alcoholic hepatitis (Maddrey score above 60). Six patients received MARS, 6 received Prometheus, and 6 received SMT (including hemodialysis). After 3 consecutive days of therapy (mean approximately 6 hours), both MARS and Prometheus reduced serum bilirubin ($p < 0.005$), and MARS increased MAP ($\Delta +9$ mmHg; $p < 0.05$) and SVRI ($\Delta +220$ dyne-s/cm⁵ per m²; $p < 0.05$) compared with Prometheus. No difference in hemodynamics was noted between Prometheus and SMT. Levels of endogenous norepinephrine, aldosterone, and vasopressin were reduced ($p < 0.05$) in the MARS group, whereas there was no statistically significant change in the Prometheus or SMT arms.

III. Single-Pass Albumin Dialysis

SPAD differs from MARS and Prometheus in that it uses a standard continuous venovenous hemodialysis (CVVHD) or venovenous hemodiafiltration system without any additional columns or circuits. Blood is dialysed against a standard dialysis solution with the addition of 4.4% albumin in the dialysate. The patient's blood is dialysed through a high-flux hollow-fibre hemodiafilter. In contrast to MARS, the albumin dialysate is not regenerated as no adsorbent columns are employed. A treatment is undertaken over 6 to 8 hours using 4.5 litres of dialysate and 700 ml of albumin.

Sauer and colleagues [32] published *in vitro* work in which the efficiency of SPAD versus MARS versus standard CVVHD was determined from plasma samples obtained from 18 patients by plasmapheresis. Ammonia, bile acids, and conjugated bilirubin were added to the patient samples and then clearance was determined. This study showed that the removal of bile acids was similar between MARS and SPAD and that SPAD removed significantly more conjugated bilirubin than MARS (both significantly greater than CVVHD).

To date, little clinical data about SPAD have been published. Seige and colleagues [33] reported that HE grade improved in three patients with AoCLF and that one patient was successfully transplanted and survived. Kreyman and colleagues [34] reported that one patient with hyperacute liver failure secondary to Wilson disease was successfully bridged to transplantation and that SPAD efficiently cleared copper and bilirubin. Currently, there have been no random-

ized controlled studies showing its biochemical, hemodynamic, or survival benefits *in vivo*.

Discussion

There continues to be great interest in and potential for the various forms of extracorporeal albumin dialysis. However, at present, we cannot make an evidence-based recommendation supporting MARS, Prometheus, or SPAD. Of the three, MARS is the best-studied albumin dialysis technology in ALF and AoCLF; however, there is a paucity of robust randomized studies, and most of the data are largely observational. Although studies in both ALF and AoCLF have shown improvement (reduction) in biochemical markers (and HE grade in AoCLF) on MARS, no conclusive mortality benefit has been demonstrated to date, but studies are currently in progress to address this issue. While promising, hemodynamic improvement on MARS has not been demonstrated in all studies. Based on two studies [24,25], bleeding appears to be a significant potential issue with MARS therapy. Clearly, larger randomized studies are needed to definitively clarify issues of hemodynamics, mortality benefit, and side effects.

Prometheus has also demonstrated improvements in biochemical but not hemodynamic or inflammatory profiles. Prometheus does appear to be safe and has not been shown to increase bleeding complications in the limited uncontrolled studies. No mortality benefit to date has been demonstrated. A large, multi-centred randomized study in patients with AoCLF is currently under way to clarify its benefits and side effect profile. Given the paucity of data for SPAD, we cannot comment on its risks and benefits.

There are many methodological limitations in the published studies to date. First, many studies did not have homogeneous study groups (that is, ALF and AoCLF) or etiologies (each often has very different prognoses). Several studies did not stratify patients based on severity of illness (for example, Child Pugh score and APACHE [Acute Physiology and Chronic Health Evaluation] score) and hence it is difficult to assess patient matching or the impact of underlying disease on patient mortality with or without treatment. Duration and number of treatments varied between studies, which may explain inconsistent biochemical and hemodynamic findings. Some studies did not clearly define adjuvant therapies in either the albumin dialysis or SMT arms. Also, co-interventions such as transfusion targets, ventilatory strategies, hemodynamic targets, and algorithms for screening and treatment of infectious diseases were often not explicitly specified. Given this heterogeneity in previous studies, it is difficult to develop evidence-based clinical (for example, HE grade) and biochemical (for example, bilirubin) criteria to define the need to initiate therapy and furthermore define the optimal duration of therapy. These issues need to be addressed in larger controlled studies in order to truly assess the impact of albumin dialysis on mortality.

One of the most important factors impacting the outcome of extracorporeal liver support is patient selection. At present, most patients being treated already have multi-organ failure and have been found to have a poor prognosis irrespective of MARS, Prometheus, or SPAD therapy (for example, many studies report a 30-day mortality of greater than 70%). In previous epidemiological studies, Jalan and colleagues [35] have noted that patients with AoCLF with the presence of organ failure (that is, Sequential Organ Failure Assessment [SOFA] score above 8) have a distinctly worse prognosis than decompensated cirrhosis patients without organ failure. Furthermore, in these AoCLF patients with a SOFA score above 8, those who previously decompensated in the previous 6 months have a much worse prognosis (mortality at 1 year of 78% versus 34%) [35]. One could speculate that selecting decompensated cirrhosis patients and ALF patients prior to the development of multi-organ failure might prove to be more beneficial.

At present, bilirubin is the most studied biochemical endpoint of albumin dialysis therapy. However, since its decline does not necessarily correlate with survival or other important clinical endpoints such as bridging to liver transplant, other surrogate markers are sorely needed. Inderbitzin and colleagues [36] showed in post-surgical patients receiving MARS (either partial hepatectomy for hepatocellular carcinoma or cholangiocarcinoma or early graft dysfunction) that the most important prognostic markers for improvement on MARS were an indocyanine green plasma disappearance rate of above 5% and Factor V levels of above 30%. This again suggests that earlier intervention will be most beneficial. This is an area that needs further exploration.

Regardless of the form of liver support, patient prognosis is universally poor if liver transplantation is not promptly available. Although a statistically significant 30-day survival benefit may be found, its clinical relevance, particularly in patients with AoCLF in the absence of transplant, is doubtful.

Conclusion

In summary, these new techniques using albumin dialysis represent potentially exciting advances in these desperately ill patients with ALF and AoCLF. The challenge upon us now is to learn how to best exploit these therapies to the patients' advantage. We need to determine which biochemical and clinical parameters correlate best with important patient outcomes such as overall survival, bridging to liver transplantation, and prevention of multi-organ failure. This information will help determine which technical refinements are most likely to be beneficial and can guide future clinical studies. Different patient subgroups are likely to have different benefits from albumin dialysis; trials should not combine ALF and AoCFL, and different etiologies will have to be evaluated separately. Adequately powered randomized controlled trials are now required to show the benefit of albumin dialysis. At this point, the appropriate comparator is

still SMT rather than head-to-head comparisons of different forms of albumin dialysis in assessing short- and long-term survival, need for liver transplantation, and prevention of multi-organ failure.

Competing interests

CJK and JW are currently involved in a multi-centred study assessing Prometheus in patients with AoCLF but have not received any financial remuneration from Fresenius AG. NG, DK, and VGB declare that they have no competing interests.

Authors' contributions

CJK reviewed original articles, drafted the manuscript, and was involved in revising the manuscript. NG and JW reviewed original articles and were involved in revising the manuscript. DK outlined the format of the review and was involved in revising the manuscript. VGB initiated the review, reviewed original articles, and was involved in revising the manuscript. All authors read and approved the final manuscript.

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