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The Molecular Adsorbents Recycling System as a Liver Support System Based on Albumin Dialysis: A Summary of Preclinical Investigations, Prospective, Randomized, Controlled Clinical Trial, and Clinical Experience from 19 Centers

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Abstract: Artificial liver support aims to prolong survival time of patients with liver failure by detoxification. Albumin as a molecular adsorbent in dialysis solution is capable of attracting even tightly albumin-bound toxins from blood into the dialysate if a specific dialysis membrane is used and if the albumin's binding sites are on-line-purified by a sorbent/dialysis-based recycling system (i.e., molecular adsorbents recycling system, or MARS). The MARS technology has been shown to remove water-soluble and albumin-bound toxins and to provide renal support in case of renal failure. Fourteen centers have reported that MARS treatment improved mental status of patients with liver failure and hepatic encephalopathy. In treating liver failure and cholestasis, MARS was associated with hemodynamic stabilization, improvement of hepatic and kidney function, and disappearance of pruritus. In hepatic failure and hepatorenal syndrome, a prospective, randomized, controlled trial of MARS treatment was able to prolong survival time significantly. MARS has been used in 26 patients with acute liver failure or primary graft dysfunction. Nineteen centers reporting on 103 patients have shown that MARS treatment is safe, easy to handle, feasible, and effective. **Key Words:** Albumin dialysis—Clinical trials—Liver failure—Liver support—Molecular adsorbents recycling system—Multicenter trials.

Hepatic failure is a clinical syndrome that results from loss of functional liver cell mass below a critical level. This may be due to toxic-, viral-, or ischemic-induced massive hepatocyte necrosis in a formerly healthy liver causing acute liver failure, or it may be due to a precipitating event that complicates chronic liver disease in a patient with already limited functional hepatic capacity. The latter is acute decompensation of chronic liver disease and is called acute on chronic liver failure. As a result, the major liver functions, particularly detoxification, synthetic functions, and metabolic regulation will be impaired to different degrees, and as such, perpetuate each other. The imbalance between the physiological needs and the functions provided by the injured liver results in major life-threatening complications of liver insufficiency such as hepatic encephalopathy and coma, jaundice and cholestasis, ascites, renal failure, bleeding, immune disorders, and sepsis.

The current standard medical therapy (SMT) involves measures to treat complications and prevent further deterioration until the precipitating event can be managed in case of acute on chronic liver failure or the liver spontaneously recovers as a possible outcome in acute liver failure. Failure of these attempts leaves liver transplantation as the only viable treatment option. However, orthotropic liver

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transplant is not readily available for most patients due to the shortage in cadaveric organs.

The management of the precipitating event of liver failure until enough liver cells can help regain its function, regenerate, or an organ becomes available for transplant, requires time. Hence, time remains the crucial factor in successfully managing liver failure. Liver support technology is evolving as different techniques to assist the remaining functional cell mass by providing specific liver functions become available. The major objective of liver support is buying time.

Earlier attempts to provide liver support included the use of several extracorporeal detoxification procedures such as hemofiltration or hemodialysis, plasma exchange, and hemoperfusion or plasma perfusion using charcoal- or polymer-based sorbents.

These procedures proved to be safe, particularly hemofiltration, which had beneficial effects in some patients with hepatic encephalopathy. However, they were not significantly effective in removing albumin-bound toxic molecules due to their high binding affinity to albumin and to their inability to permeate dialysis membranes (1).

Plasma exchange was associated with major side effects that prevented the extended use that would be necessary for effective detoxification (2).

The use of nonspecific sorbents such as charcoal or ion exchangers in direct contact with blood or plasma resulted in effective removal of toxic molecules, but was also complicated by bioincompatibility, which resulted in alarming drops in fibrinogen, and by activation of complements, which resulted in systemic inflammatory response (2–4). In addition, the direct contact between sorbents and plasma proteins has been shown to result in removal of hepatocyte growth factor (5) and a number of hormones such as growth hormone (3), triiodothyronine (T_3), tetraiodothyronine (T_4), (3,6–8), parathormone (9), testosterone, steroid hormones, and insulin (3,10,11).

Attempts to reduce these unwanted effects of direct contact between sorbents and plasma proteins involved the use of membranes that separate blood and the unspecific sorbent. One membrane used is a cellulose flat membrane that has a similar permeability to that of a standard low-flux cellulose dialyzer (12). Although it improved hepatic encephalopathy in some patients, it does not allow removal of the albumin-bound fraction of toxic molecules. In fact, bilirubin, which is a marker for albumin-bound toxins, increased during the treatment using this membrane (13).

Another membrane used had a pore size large enough to allow albumin as the toxin carrier to pass through, but had a lower sieving coefficient for large plasma proteins such as immunoglobulin M (IgM) (14). Furthermore, as many valuable molecules have a molecular weight close to albumin, there is a loss of valuable substances such as immunoglobulin G (sieving coefficient >70%), high-density lipoprotein (sieving coefficient 65%), and fibrinogen (sieving coefficient 17%) (14). Studies regarding the loss of other molecules that have similar molecular size to albumin, such as antithrombin III, transthyretin, transcortin, and so forth, and which also have high sieving coefficients, have not yet been published. Using this type of fractionated plasma separation in vivo resulted in a drop of serum bilirubin and an improvement of hepatic encephalopathy (13).

Thus, plasmasorption using albumin-permeable membranes to filtrate plasma or plasma fractions in order to perfuse it over unspecific sorbents to remove protein-bound toxins was not efficient in the management of liver failure in prospective, controlled randomized studies.

Recent developments have focused on the use of liver cells in extracorporeal systems to improve and substitute some of the liver functions during acute liver failure. As adult human hepatocytes cannot be produced in culture in adequate amounts, different systems use porcine hepatocytes (15) or human hepatoma cells (16). Two of these systems are currently being tested for their efficacy on patients with acute liver failure.

The goal of removing albumin-bound toxic molecules that accumulate in liver failure in an effective but also selective biocompatible manner has not been achieved with current conventional methods.

THE METHOD OF ALBUMIN DIALYSIS

Albumin dialysis is a new method that combines the efficacy of sorbents to remove albumin-bound molecules with the biocompatibility of the modern dialysis membrane. It is selective in removing protein-bound molecules that use albumin as a specific toxin carrier in human blood. Thus, albumin dialysis is an extracorporeal liver support system based on the concept of dialysis, using a specific membrane (Teraklin AG, Rostock, Germany, cut-off 50,000, sieving coefficient for albumin less than 0.01) and albumin as the dialysate. The albumin acts as a specific molecular adsorbent that is regenerated on-line by recirculating in a recycling system (i.e., molecular adsorbents recycling system, or MARS, trademark of Teraklin AG, Rostock, Germany). Due to the attracting effect of albumin, the system achieves high clearance of albumin-bound substances such as bile

acids and bilirubin, which are not removed by hemofiltration. The membrane used in MARS is capable of releasing the albumin-ligand complex present in the blood due to its physicochemical ability to interact with lipophilic binding domains. The membrane itself is impermeable to albumin and other valuable proteins such as hormones, clotting factors, and antithrombin III and is highly tolerated in clinical use. The two sorbent columns and the dialyzer allow the removal of both protein-bound and water-soluble toxins, thus making the system useful for patients with liver failure complicated by renal insufficiency. Furthermore, additional organ support is provided by maintaining electrolyte, acid/base, fluid balance, glucose level, and by removing ammonia, a water-soluble toxin that accumulates in liver failure.

In summary, the membrane is biocompatible, which ensures a safe long-term use with no or minimal need of anticoagulation and with minimal effect on blood cell counts, platelets, and the complement system.

RESULTS FROM LABORATORY INVESTIGATIONS

Proof of concept

In laboratory investigations, it has been shown by several groups that even tightly albumin-bound molecules such as unconjugated bilirubin can be removed by dialysis using specific albumin-impermeable dialysis membranes and an albumin-containing dialysate solution (17–20). In vitro investigations using fluorescence-labeled albumin have shown that toxins travel across the membrane, reaching the dialysate solution where they are bound by albumin (21). The driving force for the mass transport of albumin-bound molecules from the blood through the membrane is the greater availability of free binding sites of the highly purified albumin in the dialysate compartment (22).

Known protein-bound substances cleared by the MARS system

In 8 consecutive patients receiving 1 single treatment of MARS, the mean reduction of serum bilirubin as a marker for albumin-bound molecules was 35% compared to baseline (23). This was superior to the reduction rates (24%) reported by albumin-permeable membranes in fractionated plasmapheresis in vivo (13).

Furthermore, dialysis using this type of membrane and albumin in the dialysate solution increased the removal of a number of substances having a high albumin affinity including bile acids (24), benzodiazepines (25), copper (26), middle-chain fatty acids (27), arachidonic acid (28), tryptophane (21), IL-6 (29), and TNF-α (29). In addition, reduction of aromatic amino acids associated with an increase of branched-chain amino acids was observed in patients with liver failure who were treated with MARS (21).

Known water-soluble substances cleared by the MARS system

MARS involves an actual dialysis circuit containing albumin which allows the system to function as hemofiltration. This property is effective in clearing serum ammonia (24,30), creatinine (24), and urea (24) at certain flow rates.

Impact on valuable molecules

The plasma levels of proteins with a molecular weight close to albumin, such as antithrombin III, transferrin, thyroglobulin, and α_1-antitrypsin, did not change during the treatment (21,24). Other physiologically valuable substances bound to transport proteins other than albumin, such as T_3 and T_4, which are bound to thyroxin-binding globulin, also were unchanged (21).

Laboratory animal evaluation

Awad and colleagues (31) evaluated the MARS concept in an animal model of cholestatic liver failure. Dogs were studied 1 week after portocaval shunt and bile duct ligation which caused parenchymal injury and excretory failure (32). A 6 h treatment with MARS hemodiafiltration decreased bilirubin, ammonia, and aromatic amino acids.

RESULTS FROM CLINICAL TRIALS

Results in chronic liver disease complicated by hepatorenal syndrome

Two centers participated in the first prospective, randomized controlled trial to investigate the influence of albumin dialysis using MARS in patients suffering from end-stage liver disease and hepatorenal syndrome Type-I (33). A summary of baseline parameters and results is given in Table 1. All patients were Child Turquotte Class C and had elevated serum bilirubin (mean serum bilirubin >20 mg/dl). All 13 patients were oliguric or anuric and had a urine sodium <20 mmol/L, despite having adequate intravascular volume (CVP 10 mm Hg). Patients were randomized to standard medical therapy including hemodiafiltration or MARS treatment. MARS treatment was well tolerated and resulted in a significant removal of bilirubin as a marker for albumin-bound molecules. Furthermore, kidney function and creatinine levels also improved significantly in the MARS group compared to the control group. Associated with all these physiological improvements, a prolon-

TABLE 1. *A summary of clinical baseline and results of a prospective, randomized, controlled two-center trial in liver failure complicated by hepatorenal syndrome (31)*

	Control group		MARS group
Baseline			
Mean urine output		<500 ml/day; NS	
Mean CVP		>10 mm H_2O; NS	
Mean CTP		>12; NS	
Mean serum bilirubin		>20 mg/dl; NS	
Mean PT value (Quick)		<40%; NS	
Mean age		<50 years old; NS	
Gender		4/6 female/male; NS	
Results			
MAP			
Before		MAP <70 mm Hg, NS	
After	<60 mm Hg	$p < 0.05$	>80 mm Hg
Creatinine			
Before		>3 mg/dl, NS	
After	>3 mg/dl	$p < 0.05$	<3 mg/dl
PT value after treatment	Not significantly changed		Significantly increased
Bilirubin after treatment	Not significantly changed		Significantly reduced
Survival time analyis	<7 days		Significant prolongation in survival time ($p < 0.05$)

gation in survival time was achieved in the MARS group and was statistically significant (Table 1). The hemodynamic effects of the MARS treatment in end-stage liver disease were investigated in another trial (23). Eight patients suffering from acute decompensation of chronic liver disease received a single MARS treatment. All patients were Child Turcotte Class C and had a serum bilirubin higher than 15 mg/dl. Five patients had hepatorenal syndrome as well. After the treatment, the mean bilirubin was reduced to 65.4% and creatinine to 48.4% compared to baseline. There was a statistically significant improvement in the mean arterial pressure resulting from an increase of systemic vascular resistance (23). The hemodynamic improvement was associated with the reduction in plasma renin activity (23).

Results in chronic liver disease complicated by cholestasis

Because MARS has the ability to clear bilirubin and bile acids, it was used in patients with end-stage liver disease (ESLD) and cholestasis (34). Twenty-six consecutive patients with ESLD and cholestasis were included in the study after an initial trial of SMT without improvement. Their serum bilirubin was higher than 15 mg/dl, and 23 patients had hepatic encephalopathy, 11 had refractory ascites, 14 had hepatorenal syndrome, and 23 had detectable infections. Patients received treatments every day or every other day depending on a patient's condition. The mean number of treatments was 5.5 per patient. A 6 h MARS treatment resulted in significant reduction of serum bile acid and serum bilirubin levels. There was significant improvement in hepatic encephalopathy, and all patients on MARS had an improvement in their Child Turquotte Pugh score.

Similar findings were reported by another group that studied patients with ESLD and acute decompensation presenting with hepatic encephalopathy (35). The group reported reduction of serum bilirubin and ammonia levels and a considerable neurological improvement in all patients. Using central venous monitoring, they also confirmed an increase in systemic vascular resistance associated with an increase of mean arterial pressure.

Results in acute liver failure

A phase-I pilot study using MARS in acute liver failure as a bridge to liver transplant is actively recruiting patients (36). Preliminary data show that the procedure is well tolerated, the serum ammonia level decreased significantly, hepatic coma score improved, and the ratio between branched-chain and aromatic amino acids increased significantly. In addition, there was a significant increase in clotting factor VII as a marker for hepatocyte synthetic function. Of the 5 patients enrolled in this study who were United Network Organ Sharing (UNOS) status 1, 1 patient recovered his native hepatic function, and 3 patients were successfully bridged to transplantation. It is worth mentioning that one of the patients who was retransplanted was anhepatic and on MARS therapy for 70 h.

In another center using MARS in fulminant hepatitic failure, 4 patients were bridged until a transplant became available (37). This center's experience confirmed significant reduction of serum ammonia and bilirubin and neurological improvement.

Two cases with fulminant Wilson disease (26,38)

complicated by renal failure, toxic hemolysis, and hepatic encephalopathy were treated with albumin dialysis. Both patients recovered at 3 and 8 weeks, respectively, and were transplanted. The copper removal rate obtained by MARS exceeded the removal rate obtained by plasma exchange, and the renal excretion of penicillamine was used as chelator (23).

Another center reported the use of MARS in a 49-year-old patient suffering from fulminant liver failure due to acetaminophen toxicity (39). The patient had hepatic coma, increased intracranial pressure, and severe coagulopathy (INR 4.1). She was listed for liver transplantation status 1. Her course was complicated by kidney failure, acidosis, and severe hypoglycemia. MARS treatment was initiated to keep the patient alive until a liver for transplant became available. Reduction of intracranial pressure and improvement of neurological function and hemodynamic status was observed within the first 24 h after the start of treatment. After 3 days on MARS, the patient's liver function improved, and MARS was stopped. The patient recovered without need of transplantation (39).

Results in primary graft dysfunction

MARS therapy has been used in the treatment of primary graft dysfunction complicating split liver transplantation. In one center out of 4 grafts with primary graft dysfunction and cholestasis, 3 recovered, and 1 patient was retransplanted successfully (40). At another center, an infant patient with primary graft dysfunction complicating a split liver transplantation was treated with MARS (41). The patient's condition was stabilized until retransplantation 2 weeks later. Six other patients with primary graft dysfunction and bilirubin greater than 15 mg/dl were treated with MARS (37). Five grafts recovered, eliminating the need for retransplantation. In case reports from two other centers, 2 out of 3 patients were bridged to retransplantation (42,43).

Results in other applications

As a result of the effectiveness of MARS in removing molecules that accumulate in cholestasis, it has been used to treat a patient suffering from benign recurrent intrahepatic cholestasis. A 36-year-old man suffering for 20 years from attacks of cholestasis lasting 5–6 weeks and associated with intolerable pruritus received 3 single treatments. The pruritus improved clinically faster than in any of the patient's earlier attacks (44). The capability of MARS to increase systemic vascular resistance and mean arterial pressure suggested its use in patients awaiting heart transplantation whose liver failure is complicating ventricular heart failure (45). The treatment resulted in improvement in hepatic encephalopathy and a drop in bilirubin. Whether the treatment can significantly improve the clinical outcome in this group of patients is under investigation in a randomized controlled trial.

DISCUSSION

The current literature contains evidence that MARS is effective in the treatment of chronic liver disease complicated by hepatorenal syndrome and cholestasis. MARS treatment results in improvement in systemic hemodynamic status, renal function, and hepatic encephalopathy. These changes brought about improvement of the Child Turqotte Pugh score of patients.

The different mechanisms responsible for these improvements are not completely clear. However, the improvement in the outcomes of patients treated with MARS could not only be attributed to removal of bilirubin alone because bilirubin is but an indirect marker for albumin-bound molecules that accumulate in patients with liver failure and is nontoxic. A number of investigators indicate that toxic bile acids are involved in the pathophysiological changes seen in cholestasis and may be even toxic to the liver (46). The reduction of serum bile acid levels by MARS treatment was associated with a reduced toxicity of the plasma of patients if applied to primary hepatocytes in culture (34). Other molecules bound to albumin that may be involved in the clinical effects seen during MARS treatments are endogenous vasodilators such as nitric oxide (47), which has been shown to accumulate in patients with liver failure (48). Whether an endogenous vasodilator is removed by albumin dialysis or albumin dialysis removes molecules that compete with an endogenous vasodilator for binding sites has yet to be examined. The extracorporeal removal of albumin-bound molecules by MARS reduces competitors for serum albumin binding sites, and provides more available binding sites in the microcirculation for binding free toxic molecules.

CONCLUSIONS

Increasing survival time is the major goal of liver support. The ability of the current MARS technique to prolong significantly survival time in patients with hepatorenal syndrome complicating severe cholestasis has been shown in a prospective, controlled randomized trial. The use of long-term albumin dialysis to support patients awaiting elective liver transplantation in case of decompensation was reported by Seige and colleagues (49). The efficacy and cost ef-

ficiency of albumin dialysis can be improved by using sorbent-based recycling as done by the MARS technique (50). To date, more than 500 MARS treatments have been done in more than 200 patients. One hundred and three of these patients are reported in the literature. An overview of reported data is given in Table 2. Data from 19 centers reporting on 103 patients show that albumin dialysis using MARS is safe, easy to handle, and feasible. It has been shown to be effective in liver failure complicated by hepatic encephalopathy or cholestasis and has been associated with clinical improvement. A prospective, controlled randomized two-center trial has shown that MARS is able to prolong survival time significantly.

Ongoing prospective, randomized, controlled trials elucidating the efficacy and cost-effectiveness of MARS versus standard medical treatment in managing decompensated chronic liver disease are underway to determine whether MARS can shorten

TABLE 2. *A summary of multicenter clinical experiences*

Reference center	Reported indications (n)					Results
	AoC	A	PGD	Other	Total	
Awad et al. (36), Michigan	4	5			9	Neurological improvement, bridge to liver transplant (LTx), reduction of ammonia, increase of Fischer index and factor VII
Schmidt et al. (23,30), Copenhagen	8				8	Increase of SVR, MAP, and cerebral perfusion, neurological improvement, decrease of serum renin activity, bilirubin, ammonia, creatinine
Sorkin et al. (35), Tel Aviv	8				8	Neurological improvement, reduction of intracranial pressure (ICP), reduction of SjvO2, reduction of serum bilirubin, ammonia
Novelli et al. (37), Rome		4	6		10	Neurological improvement, bridge to LTx, reduction of serum ammonia, bilirubin, and INR
Stange et al. (34), Rostock	26				26	Neurological improvement, reduction of ascites, bilirubin, PT, bile acids, creatinine, and CTP
Jost et al. (42), Leipzig	7		1	3[a]	11	Bridge to LTx, decrease of PT, increase of choline esterases
Delafosse et al. (43), Lyon	1		2	2[b]	5	Neurological improvement in chronic patient
Siewert-Delle et al. (39), Göteborg		1			1	Neurological and hemodynamic improvement, reduction of ICP and INR, spontaneous recovery
Manz et al. (38), Freiburg		1			1	Bridge to elective LTx, reduction of serum copper and bilirubin in acute WD
Kreymann et al. (26), Munich		1			1	Bridge to elective LTx, reduction of serum copper and bilirubin in acute WD
Loock et al. (40), Essen			4		4	Neurological improvement, graft recovery, reduction of serum bilirubin
Kasakow et al. (41), Jena			1		1	Bridge to re-LTx in an infant (15 month old infant), reduction of serum bilirubin
Aviles et al. (51), Santa Cruz de Tenerife	3				3	Neurological improvement, disappearance of pruritus, reduction of serum bilirubin
Seige, Kreymann, et al. (49), Munich	3				3	Neurological improvement (EEG-monitored), bridge to elective LTx, reduction of bilirubin
Oliviero et al. (52), Mercurio et al. (53), Rome	1				1	Neurological improvement (decrease in resting motor threshold), reduction of ammonia, bilirubin, and bile acids
Kapoor et al. (54), London	1				1	Neurological improvement, reduction of PT and bilirubin
Ullerich et al. (55), Münster	1				1	Neurological improvement, bridge to elective LTx, reduction of bilirubin
Wilmer et al. (56), Leuven	1				1	Neurological improvement, reduction of bilirubin, bile acids, and PT
Notohamiprodjo et al. (45), Bad Oyenhausen				7[c]	7	Neurological improvement, reduction of bilirubin
Huster et al. (44), Leipzig				1[d]	1	Disappearance of pruritus, reduction of bilirubin
Total	64	12	14	13	103	

[a] 1 liver failure posttrauma; 1 Budd Chiari syndrome; 1 liver failure after hepatectomy in hepatocellular carcinoma and hepatitis B.
[b] 2 liver failure after hepatectomy.
[c] 7 liver failure secondary to right ventricular heart failure.
[d] 1 benign recurrent cholestasis (BRC).

A, acute; AoC, acute on chronic; PGD, primary graft dysfunction; MAP, mean arterial pressure; SVR, systemic vascular resistance; SjvO2, jugular vein oxygen saturation; ICP, intracranial pressure; INR, international ration; PT, prothrombin time; CTP, Child Turqotte Pugh score; WD, acute Wilson's disease.

the time to recovery and decrease morbidity and mortality.

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