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Fulminant Hepatic Failure Bridged to Liver Transplantation with a Molecular Adsorbent Recirculating System: A Single-Center Experience

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We herein describe the clinical course of a consecutive series of fulminant hepatic failure patients treated with a molecular adsorbent recirculating system (MARS), a cell-free albumin dialysis technique. From November 2000 to September 2002, seven adult patients ages 22–61 (median, 41), one male (14.2%) and six females (85.7%), affected by fulminant hepatic failure underwent seven courses (one to five sessions each, 6 hr in duration) of extracorporeal support using the MARS technique. Pre- and posttreatment blood glucose, liver function tests, ammonia, arterial lactate, electrolytes, hemodynamic parameters, arterial blood gases, liver histology, Glasgow Coma Scale, and coagulation studies were reviewed. No adverse side effects such as generalized bleeding on noncardiogenic pulmonary edema, often seen during MARS treatment, occurred in the patients included in this study. Six patients (85.7%) are currently alive and well, and one (14.2%) died. Four patients (57%) were successfully bridged (two patients in 1 day and two other patients in 4 days) to liver transplantation, while two (5%) recovered fully without transplantation. All the measured variables stabilized after commencement of the MARS. No differences were noted between the pre- and the post-MARS histology. We conclude that the MARS is a safe, temporary life support mechanism for patients awaiting liver transplantation or recovering from fulminant hepatic failure.

KEY WORDS: albumin; dialysis; extracorporeal liver assist device; fulminant hepatitis.

A molecular adsorbent recirculating system (MARS; Teraklin, Aktiengesellschaft, Rostok, Germany) is an artificial liver support system, first introduced into clinical practice in 1993 (1). In contrast to bioartificial liver support systems, which replace some of the metabolic and synthetic functions of the liver by means of established hepatocyte or hepatoblastoma cell lines (2), MARS aims only at clearing the blood of metabolic waste products normally metabolized by the liver. It is, essentially, a modified dialysis system, employing an albumin-containing dialysate that is recirculated and perfused in-line through charcoal and anion exchanger columns. This effects the removal of albumin-bound toxins like aromatic amino acids and their metabolites, conjugated bilirubin, bile acids, phenols, short- and middle-chain fatty acids, copper, mercaptans, cytokines, tryptophan, tumor necrosis factor-α, interleukin-6, and diazepam together with free solutes like ammonia, creatinine, and urea that are removed by

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TABLE 1. PATIENT AND LABORATORY DATA AT HOSPITAL ADMISSION

No.	*Sex/age*	*Diagnosis*	*Outcome/no. of MARS sessions*	*Follow-up (days)*	*Total bilirubin (mg/dl)*	*AST (IU/L)*	*ALT (IU/L)*	*γGT (IU/L)*	*Albumin (g)*	*PT (%)*
1	F/30	FHF/HBV	Died/2	0	7.41	789	2223	44	3.5	28
2	F/29	FHF/HBV	Alive, transplanted/4	820	6.97	289	1120	25	3.4	28
3	F/22	FHF/nimesulide	Alive, transplanted/1	393	13.13	209	254	48	3.8	30
4	F/51	FHF/HBV	Alive, transplanted/1	366	11.65	1239	1986	60	3	38.6
5	F/61	FHF/HBV	Alive, transplanted/4	218	17.01	749	1519	51	3	39.6
6	F/41	FHF/HBV	Alive/4	184	9.94	455	1730	51	3.1	30
7	M/50	FHF/HBV	Alive/5	180	12.08	638	2308	30	2.8	24.1

Note. AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase; PT, prothrombin time; FHF, fulminant hepatic failure; HBV, hepatitis B virus.

standard dialysis (1, 3). Most experience with the MARS has shown specific efficacy in the treatment of acute-on-chronic hepatic failure, where it improves cerebral blood flow, hemodynamic status, liver and renal function, survival (4–6), and intractable pruritus (7). The MARS maintains electrolyte homeostasis (8) but may worsen coagulopathy (9) and be the cause of noncardiogenic pulmonary edema (10).

Fulminant hepatic failure (FHF) is defined as acute encephalopathy and coagulopathy in the setting of acute liver disease where altered mental status develops within 8 weeks of the onset of illness in a person without antecedent liver disease (11). The mortality rate in the course of acute liver failure is reported to be >70% (12, 13). Liver transplantation (LTx) is a well-accepted therapy for FHF (14). However, due to lack of organ availability, it is not always possible to transplant patients with FHF. Therefore, several types of supporting systems (artificial liver/bioartificial liver) have been developed to bridge these patients to LTx or, if possible, promote spontaneous recovery (2, 15–20).

The MARS has been used in the course of FHF (21); however, changes in liver histology and their correlation with the Glasgow Coma Scale (GCS) and prothrombin time, the two major clinical indicator of disease progression, have not been addressed before.

FHF is characterized by several biochemical derangements such as acidosis (12), hypophosphatemia, and hypoglycemia (22). The degree of these derangements is, at least theoretically, related to the grade of liver necrosis. Transjugular liver biopsy is the method of choice to obtain liver tissue for histology in patients with FHF and to quantitate the degree of liver injury (23).

METHODS

Data were retrospectively collected from a consecutive series of patients with FHF admitted to the Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy, from November 2000 to September 2002, who underwent MARS while awaiting LTx or recovery (follow-up, 1155 days; range, 455–1155 days). Informed consent for MARS treatment and LTx was obtained from next of kin.

Seven adult patients (nos. 1 to 7), one male (14.2%) and six females (85.7%), ages 22–61 years (median, 41 years) underwent seven courses (one to five sessions each) of MARS. Demographics are listed in Table 1.

Patient 1 developed fulminant hepatitis B. The patient was transported to our center emergently in stage 4 coma (Figure 1) and died of brain herniation a few hours before LTx.

Hepatitis B virus (HBV) was the cause of FHF in patient 2. The patient was emergently transported to our center in stage 3 coma (Figure 1) and underwent the first LTx 5 days after the admission. The patient developed primary non function and 2 days later was successfully retransplanted. She is alive and well 38 months after the second LTx.

Patient 3 developed drug-related (nimesulide) FHF. The patient was emergently transported to our center awake and alert but went on to stage 3 coma 24 hr later (Figure 1). She was successfully transplanted 2 days following admission to our facility. She is alive and well 24 months after LTx.

Patient 4 developed HBV-related FHF. The patient was emergently transported to our center awake and alert and remained so, despite 95% liver necrosis, until LTx, which occurred 2 days after the admission. This patient is alive and well 23 months after LTx.

Patient 5 developed HBV-related FHF. The patient was emergently transported to our center in stage 3 coma and underwent two LTx during the same procedure, 5 days after admission. The first graft, a very marginal one, performed on an emergency basis, underwent primary nonfunction immediately after reperfusion, with about 80% hepatocyte necrosis. A second cadaveric donor became available at the time of reperfusion of the first graft. The patient was, therefore, immediately retransplanted. She is alive and well 18 months after LTx.

Patient 6 developed HBV-related FHF. She underwent four MARS treatments before showing clinical recovery from the acute event. Due to her dramatic clinical improvement following the first MARS treatment and despite 50% necrosis at the transjugular liver biopsy, the decision was made not to proceed with the transplant. The patient is alive and well 16 months after the last MARS session.

Patient 7 developed HBV-related FHF. He was never placed on the waiting list for LTx because he was diagnosed with colon cancer 12 months prior to his evaluation. The patient was emergently transported to our center in stage 3 coma and underwent a total of five MARS treatments before showing clinical

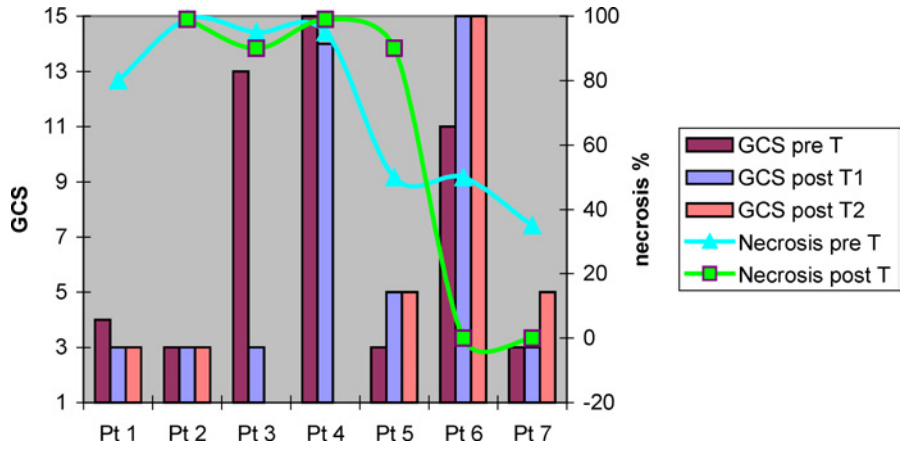

Fig 1. Correlation between Glasgow Coma Scale (GCS) and necrosis during molecular adsorbent recirculating system (MARS) treatment (T). GCA is represented by bars. The percentage of liver necrosis is represented by lines. Each group of bars refers to a single patient (Pt). The first bar for each patient identifies the pre-MARS GCS; the following bars in each group represent the GCS after each MARS session for up to three sessions. The line with triangles represents the percentage liver necrosis before MARS commencement. The line with squares represents the percentage liver necrosis on the explanted liver or (for patients 6 and 7), at recovery after the acute event.

amelioration. He is alive and well 15 months after the last MARS session.

Our pretransplant workup includes transjugular liver biopsy for those patients fulfilling the O'Grady criteria for FHF (11) at hospital presentation. In fact emergent listing for LTx and treatment with MARS, while waiting for LTx, was prompted for those patients showing $\geq$50% liver necrosis at liver histology.

Exclusion criteria from MARS and/or LTx candidacy were culture-proven sepsis and/or <50% liver necrosis. In the intensive care unit, before starting MARS, full patient monitoring was instituted, including central venous pressure, Swan-Ganz catheter placement, and a systemic arterial line. Due to on-site unavailability of technical expertise in positioning epidural probes for intracranial pressure monitoring, this parameter was not followed.

Each course of MARS was intended to consist of seven treatment sessions, 6 hr in duration (none of them had to be terminated in advance), on consecutive days. However, none of the patients completed the prescribed course (seven sessions) due to transplantation, death, or significant clinical improvement. If a liver became available while the patient was on MARS, the transplant was started after the 6-hr session was completed.

MARS treatment was performed through a hemodialysis double-lumen catheter, as previously described (24). Priming of the extracorporeal circuit with a heparinized saline solution (1000 U of heparin sulfate/liter) was carried out before MARS commencement. The extracorporeal blood circuit was driven by a standard dialysis machine (D-85716; Baxter, Unterschleibheim, Germany) at a flow rate of 100 ml/min initially, increased to 200 ml/min if the patient remained hemodynamically stable. The aim of this study was the assessment of the safety and efficacy of MARS in patients with FHF. During MARS therapy all patients were closely monitored for disturbances in electrolytes, glucose level, coagulation, and blood gas exchanges. These derangements, if present, were treated as indicated.

Pre- and post-MARS blood glucose, liver function tests (total bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase), ammonia, arterial lactate, electrolytes (sodium, potassium, chloride, calcium, phosphorus, and magnesium as well as the ionized fraction of calcium and magnesium), hemodynamic parameters (systemic blood pressure, central venous pressure, pulmonary arterial pressures, cardiac output, cardiac index, systemic vascular resistance index), arterial blood gas, GCS, and coagulation studies (platelet count, prothrombin time, international standardized ratio) were used for comparison.

Liver histology was used to quantitate the percentage of necrosis. Post-MARS liver histology on the native liver, obtained at the time of LTx, and percutaneous liver biopsies, performed after recovery from the acute event for patients 6 and 7 (those recovered without LTx), were used for comparison with pre-MARS liver histology. Patient 1 died before transplantation, and autopsy consent was denied; therefore, post-MARS liver histology for patient 1 was not available for this study.

Data are presented as mean $\pm$ standard deviation. Blood samples for laboratory tests were collected immediately before and immediately after each MARS session.

RESULTS

Six patients (85.7%) survived to be discharged from the hospital and they are all alive and well 15 months after the last MARS session. One patient (14.2%) died of brain herniation while our team was recovering a liver from an organ donor. Four patients (57%) were successfully bridged, using MARS, to LTx, and two (28.5%) recovered fully without transplantation.

Biochemical Effect of MARS Treatment. Pre- and post-MARS serum electrolyte concentration remained remarkably stable (data not shown).

TABLE 2. CHANGE IN TOTAL BILIRUBIN (MG/DL)

Patient no.	*Pre-MARS total bilirubin*	*Post-MARS session 1 total bilirubin*	*Post-MARS session 2 total bilirubin*	*Post-MARS session 3 total bilirubin*	*Post-MARS session 4 total bilirubin*
1	7.41	8.48	8.91	8.14	7.31
2	6.97	8.33	7.88	6.78	6.72
3	13.13	10.06	11.29	—	—
4	11.65	10.83	—	—	—
5	17.01	12.17	—	–	—
6	9.94	8.10	—	—	—
7	12.08	12.03	—	—	—

Hypoglycemia is common in FHF, being due to altered gluconeogenesis in the failing liver with inadequate hepatic uptake of insulin, heading to increased peripheral insulin levels (22). In our series patients treated with MARS showed remarkably stable blood glucose during treatments (data not shown).

Total bilirubin (Table 2), transaminases, γ-glutamyl transpeptidase, and ammonia, as previously reported (1, 3), all improved with MARS (data not shown).

The MARS reduced the arterial blood lactate level in FHF (Figure 2).

Effect of MARS Treatment on Mental Status. Those patients that recovered fully without LTx (patients 6 and 7, Table 1) showed a steady improvement in GCS after each MARS sessions (Figure 1). Patient 5, in Table 1, also showed a significant improvement in GCS after the first MARS session (Figure 1); however, at the time of LTx liver necrosis was >95% (Table 3).

Hemodynamic Effect of MARS Treatment. Patients with FHF tend to be hemodynamically unstable, with a low systemic vascular resistance index and a hyperdynamic circulation (30). None of the patients treated in our series required vasopressor infusion before transplantation and all remained hemodynamically stable throughout MARS treatment. Amelioration of the hyperdynamic state was supported by the elevation of the systemic vascular resistance index and mean arterial pressure and the reduced cardiac index (Figure 3).

Effect of MARS Treatment on Gas Exchange. Pre- and post-MARS treatment, blood gas remained remarkable stable (data not shown).

Histological Effect of MARS Treatment. No signs indicative of the MARS affecting liver histology were noted when pre- and post-MARS liver specimens were compared in patients who underwent LTx (Table 3; comparison is between histology at the time of transjugular liver biopsy and histology of the explanted liver). Four of five patients who underwent LTx showed ≥80% liver necrosis at transjugular liver biopsy (Table 3). Patients 6 and 7 (those recovered without LTx) showed 50% liver necrosis at admission to the hospital and absence of necrosis at recovery following the last MARS treatment (Table 3).

Effect of MARS Treatment on Blood Coagulation. All patients were coagulophatic at admission and remained so, despite aggressive medical correction throughout their stay in the intensive care unit, which consisted of continuous infusion of fresh-frozen plasma at the rate of 30 ml/hr. Although one could postulate that the percentage of necrotic liver tissue correlates directly with all the commonly seen clinical and biochemical derangements of FHF, we did not find any relationship between necrosis

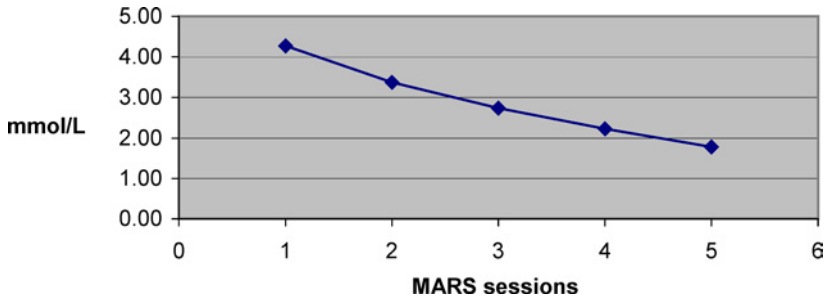

Fig 2. Pattern of arterial lactate during molecular adsorbent recirculating system (MARS) treatment in fulminant hepatic failure (FHF). The *x* axis represents the mean arterial lactate concentration (mM); the *y* axis represents the different MARS sessions.

TABLE 3. PRE- AND POST-MARS LIVER HISTOLOGY

Patient no.	*Pre-MARS necrosis*	*Post-MARS necrosis*
1	80%	n/a
2	100% (massive)	100% (massive)
3	95 %	90%
4	95%	100% (massive)
5	50%	>95% (submassive)
6	50%	0%
7	50%	0%

and prothrombin time (Figure 4). Prothrombin time before and after MARS is reported in Figure 4.

DISCUSSION

Paradoxically the major limitation of this study is the availability of LTx, which occurs at various times after commencement of treatment and, therefore, causes difficulties in designing scientifically reproducible clinical trials.

We cannot exclude that some of our observed results, in terms of biochemical homeostasis/hemodynamic stability during treatment of FHF with the MARS, may be secondary to aggressive medical management in the intensive care unit, preceding transplantation. However, there have been proven effects, in different models, of MARS ameliorating parameters not otherwise influenced by medical therapy, such as total bilirubin (1, 3) and blood lactate levels (24). The liver is the principal organ for lactate metabolism, accounting for 50% of the whole-body lactate clearance and utilization, and hence participates in the regulation of serum lactate concentrations (25, 26). Moreover, in the LTx literature, with both cadaveric and living donor, it has been demonstrated that the rate of lactate elimination after reperfusion of the transplanted liver represents one of the most sensitive and reliable indicators of hepatic graft function (27–29). Therefore, we believe that the decreased lactate level during MARS treatment of patients with FHF indicates improvement (Figure 2). It is uncertain whether, in our series, MARS is responsible for the observed decreased transaminases, because normalization of liver enzymes in the late phase of FHF is typically seen after massive liver necrosis.

However, it appears that the degree of liver necrosis, GCS, and timing of MARS commencement may play a role in the outcome of FHF. In patient 5 we observed GCS improvement after MARS commencement (Figure 1), despite ongoing liver necrosis (>95% in the explanted liver; Table 2). The same was also observed in patients 6 and 7 (who recovered without LTx) (Figure 1). We believe that the common denominator for these three patients was the 50% liver necrosis at the time of MARS commencement. During FHF, coma is the antecedent of brain herniation, and the various degrees of mental status changes observed are, in fact, strictly related to the amount of liver cells death and the consequent toxin load present in the bloodstream (11, 22, 27). There is notable evidence that MARS

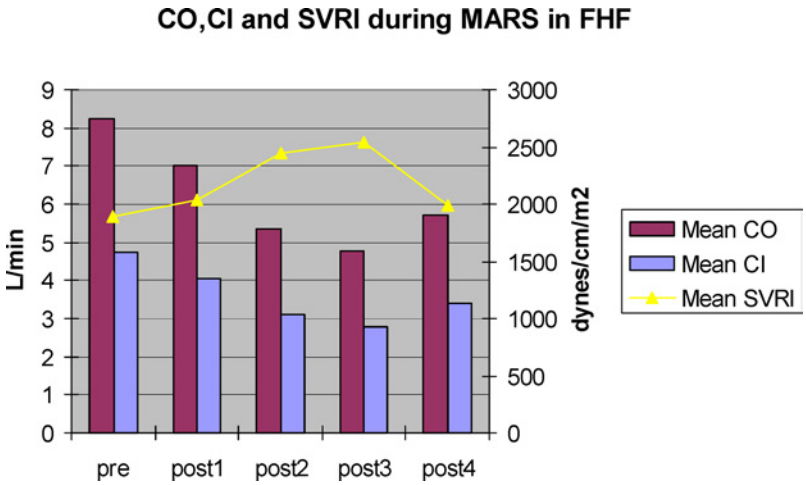

Fig 3. Cariac output (CO), cardiac index (CI), and systemic vascular resistance index (SVRI) during molecular adsorbent recirculating system (MARS) treatment in fulminant hepatic failure (FHF). Mean CO and CI are represented by bars of different colors. Their unit of measure is liters per minute, which is reported at the left. The mean SVRI is represented by the line. The unit of measure is dynes per centimeter per square meter, which is reported at the right. The first set of bars represents pre-MARS values, whereas the following sets represent post-MARS values from session 1 to session 4.

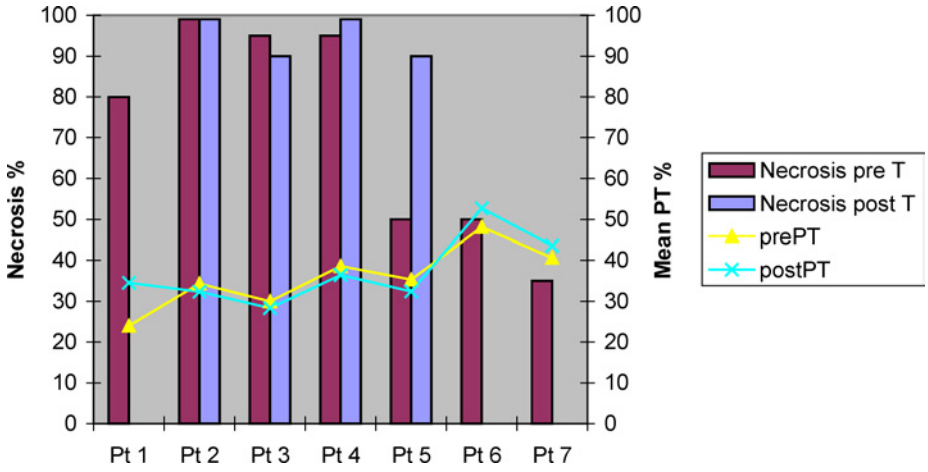

Fig 4. Correlation between prothrombin time (PT) and necrosis during MARS. Bars represent pre- and post-MARS percentage liver necrosis, whereas lines indicate PT. The line with triangles represents the pre-MARS prothrombin time; the line with Xs, the post-MARS prothrombin time. Pt, patient; T, treatment.

is able to remove these toxins (1, 3); therefore, based on our data, we postulate that if MARS treatment is started before liver necrosis exceeds 50%, brain herniation can be delayed.

A common criticism of transjugular liver biopsy in the course of FHF is that it represents a random liver biopsy, and as such it does not reflect the real percentage of liver necrosis present in the whole liver. However, 75% of the patients in our series who were transplanted (patients 2 to 4; Table 3) showed a sensitive correlation between pre- and posttransplant amount of liver necrosis. Therefore, we believe that the percentage liver necrosis seen at transjugular liver biopsy should be used as a clinical guidance toward transplantation. We did not expect any histological change after MARS treatment because of the very few treatment sessions and the short time allowed between histological observations. For other reasons (few MARS sessions and long interval between histological observations),we believe that the absence of necrosis in the post-MARS liver histology for patients 6 and 7 was not a consequence of MARS treatment. It was expression of healing from FHF.

Obviously, each patient in our series was treated with a different number of MARS sessions because suitable organ donors became available at different times during MARS treatment for the different patients. Nonetheless, in our small series, MARS treatment was found to be safe and efficacious for maintaining stability in patients diagnosed with FHF and awaiting LTx. Our result suggest that MARS delayed central nervous system catastrophe by clearing the toxin load typical of FHF, thus allowing more time for successful bridging to LTx.

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