Molecular Adsorbents Recirculating System in Patients with Severe Liver Failure. Experience of a Single Romanian Centre

Elena-Emanuela Rusu, Mihai Voiculescu, Diana-Silvia Zilisteanu, Gener Ismail

Center of Internal Medicine and Nephrology, Fundeni Clinical Institute, Bucharest, Romania.

Abstract

Aim: This is a retrospective, observational study regarding the experience of the Fundeni Clinical Institute in the application of the Molecular Adsorbents Recirculating System in patients with liver failure. **Method**: From January 2002 until December 2007, we performed 50 MARS sessions in 27 patients, mean age 38.96 ± 19.58 years. The etiology of liver failure was as follows: acute liver failure (ALF) in 7 patients, acute-on-chronic liver failure (AoCLF) in 10 patients, post-liver transplantation in 8 patients, and post-hepatectomy in 2 patients. **Results**: We noticed the following clinical effects: improvement in general condition, in neurological status, marked regression of jaundice and pruritus, improvement in renal function and in hemodynamic status. Of the 7 patients with ALF, 3 patients (42.8 %) survived due to their own liver recovery. Only 2 patients (20%) with AoCLF survived. In this group, one patient was transplanted, one patient is alive, and the mean survival of the remaining patients was 24.5 ± 34.6 days. In the post-liver transplantation group, one patient was retransplanted, one patient is alive and the mean survival of the other 6 patients was 28.5 ± 39.8 days. One patient with post-hepatectomy liver failure presented spontaneous liver recovery. **Conclusion**: MARS therapy was well tolerated by the patients. MARS therapy efficiently removed water soluble and albumin-bound toxins. The unfavorable prognostic factors were the association with multi organ failure and sepsis.

Key words

Liver failure – MARS – liver transplantation.

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Address for correspondence: Mihai Voiculescu, MD, PhD
Center of Internal Medicine and Nephrology, Fundeni Clinical Institute
258 Fundeni Street, sector 2
Bucharest, Romania
E-mail: mihaiv45@gmail.com

Introduction

Acute liver failure (ALF) and acute-on-chronic liver failure (AoCLF) are associated with a high morbidity and mortality. Acute liver failure is defined as a condition in which the rapid deterioration of liver function results in altered mental performance and severe coagulopathy in previously healthy individuals. Patients considered to have AoCLF are those with previously well-compensated chronic liver disease in whom acute decompensation of liver function has occurred due to the effects of a precipitating event [1, 2]. The accumulation of toxins in liver failure seems to be an important mechanism responsible for the development of life-threatening complications [1, 3, 4]. The current management of ALF and AoCLF aims to optimise the patients' clinical and biological status and to create a bridge to liver regeneration or transplantation.

The Molecular Adsorbents Recirculating System (MARS) is an artificial liver support system that combines the selective removal of both albumin-bound toxins and water-soluble toxins. The patient's blood is dialyzed across a special hollow fiber membrane by a recirculating human albumin solution. The solution is regenerated on-line in a closed circuit by passage on charcoal and ion-exchange columns (hepatic detoxification) and is itself dialyzed by a bicarbonate dialysate (renal detoxification). The albumin-bound toxins accumulating in liver failure have hepatotoxic potential and damage kidney function, bone marrow activity, and cardiovascular tone. The removal of protein-bound as well as of water-soluble toxins provides better conditions for liver recovery and reduces plasma toxicity. Due to its high detoxifying properties, MARS is capable of temporary improving end-organ function in liver failure [5, 6].

Methods

Patients

We performed a retrospective, observational study of the patients with liver failure treated by the Molecular Adsorbents Recirculating System in the Fundeni Clinical Institute.

Between January 2002 and December 2007, 27 patients with severe liver failure were treated, males/females = 13/14, 7 children and 20 adults, mean age 38.9 ± 19.5 (range 3 - 61 years).

We divided the patients in four groups according to the indication of MARS therapy: ALF (7 patients), AoCLF (10 patients), post-liver transplantation (8 patients), and post-hepatectomy (2 patients). In the AoCLF group all patients presented cirrhosis with at least 7 points according to the Child-Turcotte-Pugh Index and a superimposed acute liver injury leading to decompensation. They fulfilled the inclusion criteria of total bilirubinemia ≥10 mg/dl and at least one of the following: hepatic encephalopathy (HE) ≥ grade II, hepatorenal syndrome. For ALF patients, the indications for MARS therapy were: hyperbilirubinemia (≥ 5 mg/dl) and HE ≥ grade I. Patients with post transplant liver failure with hepatic chronic rejection received MARS treatment if they presented serum bilirubin level ≥10 mg/dl. The patients with post transplantation acute liver failure presented the same inclusion criteria as ALF patients. Those with post-hepatectomy presented rapidly progressive hepatic failure with serum bilirubin level ≥10 mg/dl.

Patients received a standard medical therapy and etiologic treatment if possible, and were supported according to their clinical condition, including mechanical ventilation, inotrope drugs, stimulants for diuresis and dialysis or hemofiltration. Management included close monitoring of glucose levels, ionic balance, administration of proton pump inhibitors, lactulose, rifaximine. In the ALF group, there were three patients with acute hepatitis B and two patients with hepatitis B flares. One patient with acute hepatitis B was treated with lamivudine and entecavir. Both patients with hepatitis B flares were treated with lamivudine. In the AoCLF group, the etiology of cirrhosis was chronic hepatitis B and D in one case. We also administered corticosteroids in some patients with ALF or in those with AoCLF having acute alcoholic hepatitis as the precipitating event. All patients received large broad-spectrum antibiotic prophylaxis and were actively diagnosed and treated in case of positive cultures. Eight liver transplanted patients received immunosuppressive drugs.

The decision to start the MARS treatment for patients with AoCLF or ALF was made by a team of skilled specialists in hepatology, intensive care, nephrology. For the patients with post-transplantation hepatic failure, a liver transplant surgeon joined the team. Patients considered for MARS therapy were evaluated for liver transplantation or whether they had already been on the list for liver transplantation or re-transplantation.

All procedures were initiated after an informed and written consent had been obtained from a relative of the patient.

Method

The MARS monitor (Teraklin AG, Rostock, Germany) was used with a continuous veno-venous hemodialysis machine (Fresenius ADM08/ABM, Germany). In all patients we used a veno-venous access, with a double lumen catheter placed in the femoral vein or in the internal jugular vein. The blood flow was 50 – 80 ml/min for paediatric patients and 150 – 175 ml/min for adult patients. Variations among patients within the same age group were decided according to the hemodynamic status of each case. The flow in the albumin dialysate circuit ranged between 150 and 250 ml/min and the dialysate flow ranged between 1 and 3 l/h.

In order to prevent metabolic acidosis, we used a dialysate with a bicarbonate-based buffer system. A continuous infusion of standard heparin was necessary during treatment (except for three MARS procedures) to prevent clotting of the extracorporeal circuit. Anticoagulation was obtained using un-fractioned heparin (UH), administered in an initial bolus of 20-50 UI/kg body followed by continuous infusion, with a target activated coagulation time (ACT) of 180-220 seconds.

Statistical analysis

Results were analysed by SPSS version 12.0. All data are presented as mean ± SD. Two-tailed testing with $p < 0.05$ was considered statistically significant.

Results

Each patient received one to six treatments. The mean time per procedure was 10.4 ± 4.6 hours.

Before starting MARS procedures all patients presented severe cholestatic syndrome, and decreased hepatic synthesis function. Eight patients (29.6%) presented multiorgan dysfunction and six patients (22.2%) had sepsis. Eight patients had renal impairment and four of them were anuric. In three anuric patients with post-transplantation acute liver failure, hemofiltration or hemodialysis were also performed. In these three patients, the mean survival was 4.67 ±1.52 days. If we consider the patients who received only MARS as extracorporeal therapy, the mean survival was 32.53±57.82 days.

From the 17 patients presenting grade II or III HE, 6 patients required mechanical ventilation. Three patients needed vasopressor support.

MARS therapy was well tolerated in all cases, with no major incidents. We noticed favourable clinical effects and improvement of biological parameters. The hepatic synthetic function did not change significantly after treatment. A transient thrombocytopenia was observed as a side effect. We found that un-fractioned heparin (UH) infusion was necessary during MARS treatments, with the exception of three MARS sessions. UH infusion rate was on average 778 ± 415 UI/h. In 17 cases (34%) we recorded bleeding events during MARS therapy: mild bleedings in 12 cases and severe bleedings in 5 cases (4 gastrointestinal bleedings). None of them required other interventions except blood transfusions. Five out of eight patients with multiorgan failure had bleeding events during MARS therapy: mild in four cases and severe in one case. All were managed without interrupting the MARS treatment.

The presence of hemorrhagic events correlated with sepsis ($r = 0.369$, $p = 0.011$), but not with coagulation status ($r = 0.155$, $p = 0.298$) or heparin dose ($r = 0.122$, $p = 0.414$).

Three mild bleeding complications and one severe bleeding in four patients with sepsis were observed. The patient with severe bleeding required two units of packed red blood cells. These patients associated intravascular disseminated coagulopathy and a decrease in platelet counts before starting MARS therapy. In 4 cases (8%), we experienced circuit failure due to clotting. Seven patients presented positive cultures before MARS therapy, while in five patients positive cultures were evidenced after MARS treatment. The bacteria responsible for infections were Gram positive in 2 cases, Gram negative in 9 cases and fungi in 4 cases. ANOVA and T-Test analysis did not show significant differences regarding the presence of positive cultures between groups of patients. We noticed an increased number of positive cultures in the post-transplantation group, with a mean of positive cultures of 1.25. In the ALF group we calculated a mean of 0.71; in the AoCLF group the mean was 0.4. In the post-hepatectomy group none of the patients presented positive cultures. The presence of concomitant multiple organ failure and sepsis was found to be a negative prognosis factor for patients supported with MARS.

Patients with acute liver failure

The etiology of the 7 patients with ALF was: acute hepatitis B in 3 patients, acute exacerbations of chronic hepatitis B in 2 patients, acute Wilson disease in 1 patient, and acute acetaminophen intoxication in 1 patient. The mean age of the patients was 31.0 ± 22.2 years; five of them were females. Three were pediatric patients. One of the patients was receiving mechanical ventilation for grade IV HE at the time MARS treatment was started, another patient presented grade III HE and the other one, grade II HE. They underwent 1 or 2 MARS treatment sessions; mean time per procedure was 9.9 ± 4.8 hours (range 4 – 18 hours). The changes in laboratory and clinical parameters are shown in Table I. Only one significant improvement of HE grade was observed. No significant improvement in cholestasis or transaminase levels, in liver synthesis function and MELD score was noted. We found a significant drop in hemoglobin, as a complication of MARS therapy.

Of the patients with ALF, 3 patients (42.8 %) survived due to their own liver recovery. The 13-year-old patient with paracetamol intoxication and another 17-year-old pediatric patient with acute hepatitis B, made spontaneous recoveries, without transplantation [7]. Both patients have normal liver function at two years of follow-up. The patient with hepatitis B flares who was treated with lamivudine presented compensated liver function at 3 years post-discharge. Of the other four patients, one patient died because of a cerebral edema, one from a fungal infection and sepsis and two patients from multiple organ failure. Their mean survival rate was 10.2 ± 8.4 days (range 3 – 21 days).

Patients with acute-on-chronic liver failure

The etiology of AoCLF was as follows: alcoholic liver disease in six patients, and chronic hepatitis B and D, chronic hepatitis C plus alcohol, Wilson disease and primary biliary cirrhosis, each in one patient. The mean age in this group of patients was 50.1 ± 9.8 years. Precipitating events were: acute alcoholic hepatitis in 4 cases, infection in 3 cases, diazepam intoxication in 1 case, hepatorenal syndrome in 1 case and gastrointestinal bleeding in 1 case. Two patients presented grade III HE and the others grade II HE when MARS treatment was started.

They underwent 1.9 ± 1.2 (range 1 – 5) MARS treatment sessions; mean time per procedure was 10.4 ± 4.7 hours (range 6 – 20 hours). Table II shows the MARS treatment results. A significant improvement in bilirubin and creatinine levels after MARS therapy was observed. However, no significant improvement in the other clinical and biological parameters was noticed.

Table I. Laboratory and clinical parameters before and after MARS in the ALF group

Parameter (Unit)	Before MARS	After MARS
Total bilirubin (mg/dl)	20.5 ± 10.1	13.8 ± 6.9
Creatinine (mg/dl)	0.8 ± 0.2	0.6 ± 0.3
Platelets (x109/l)	85.2 ± 62.6	5.7 ± 47.6
Hemoglobin (g/dl)	11.6 ± 1.6	9.9 ± 1.0*
ALT (U/l)	1268.0 ± 1929.4	907.1 ± 1507.8
AST (U/l)	808.2 ± 1858.6	273.7 ± 465.0
Prothrombin activity (%)	32.4 ± 9.3	32.3 ± 6.9
Fibrinogen (mg/dl)	141.0 ± 25.6	128.3± 4.7
Albumin (g/dl)	2.6 ± 0.7	2.7 ± 0.7
Mean arterial pressure (mmHg)	91.3 ± 14.8	94.4 ± 12.8
Grade of encephalopathy	2.3 ± 0.7	1.7 ± 1.0*
MELD score	24.2 ± 6.3	21.3 ± 7.1

* $P < 0.05$

Table II. Laboratory and clinical parameters before and after MARS in the AoCLF group

Parameter (Unit)	Before MARS	After MARS
Total bilirubin (mg/dl)	6.4 ± 15.0	15.3 ± 6.6*
Creatinine (mg/dl)	1.3 ± 1.1	0.9 ± 0.7*
Lactate (mmol/l)	3.1 ± 1.7	1.7 ± 0.8
Sodium (mmol/l)	129.9 ± 8.6	133.0 ± 4.4
Platelets (x109/l)	122.2 ± 109.1	87.3 ± 43.8
Hemoglobin (g/dl)	8.6 ± 1.5	8.7 ± 1.6
Fibrinogen (mg/dl)	174.2 ± 35.9	165.0 ± 21.3
Prothrombin activity (%)	43.6 ± 8.6	39.2 ± 13.3
Albumin (g/dl)	2.3 ± 0.5	2.5 ± 0.5
Mean arterial pressure (mmHg)	85.2 ± 15.6	89.7 ± 14.1
MELD score	28.5 ± 6.5	26.4 ± 6.5

*$P < 0.05$

In this group, only 2 patients (20%) survived: one patient with primary biliary cirrhosis underwent deceased donor liver transplantation and one patient was discharged from hospital and he was well 5 months later, at his last review. For none of the remaining eight patients a suitable liver donor was found. Two patients have initially restored the state of hepatic compensation, but they died 17 days later from bacterial pneumonia, followed by sepsis, respectively

107 days from spontaneous bacterial peritonitis which eventually deteriorated to sepsis. The mean survival rate of AoCLF patients on the liver transplantation waiting list was 24.5 ± 34.6 days.

Patients with post-transplantation liver failure

The etiology of post-transplantation liver failure was as follows: acute liver failure (3 patients), hepatic chronic rejection (2 patients), and recurrence of hepatitis C (1 patient), reactivation of autoimmune hepatitis (1 patient) and graft dysfunction (1 patient). The mean age of the patients was 24.5 ± 19.3 years (range 3 – 49 years); four of the patients were children. Five patients required mechanical ventilation at the beginning of MARS procedures. Three patients presented grade II HE and for the other, the HE could not be evaluated. Four patients had renal impairment and three of them were anuric. Three patients needed vasopressor support, four presented multiorgan dysfunction and the other three had sepsis.

There was significant improvement in total bilirubin, creatinine, lactate, and sodium values (Table III). All the anuric patients increased the urine output during MARS therapy. There was a significant improvement of mean arterial pressure and vasopressor support was no longer necessary in two cases after MARS therapy. There was no significant improvement in the MELD score, and the HE could not be evaluated in many cases, because patients continued to require mechanical ventilation. A significant drop in hemoglobin and platelets count was also noted. Four patients needed transfusion with erythrocytes concentrate and/or thrombocytes concentrate.

Table III. Laboratory and clinical parameters before and after MARS in the post-transplantation group

Parameter (Unit)	Before MARS	After MARS
Total bilirubin (mg/dl)	35.6 ± 17.5	20.2 ± 11.0*
Creatinine (mg/dl	1.0 ± 0.8	0.5 ± 0.3*
Lactate (mmol/l)	4.9 ± 4.1	2.7 ± 2.6*
Sodium (mmol/l)	136 ± 4.3	138 ± 4.4*
Platelets (x109/l)	116.7 ± 100.2	89.7 ± 76.0*
Hemoglobin (g/dl)	7.5 ± 2.9	6.2 ± 2.4*
Prothrombin activity (%)	55.4 ± 26.0	53.7 ± 25.6
Albumin (g/dl)	3.2 ± 0.5	3.2 ± 0.6
Mean arterial pressure (mmHg)	75.1 ± 12.1	83.8 ± 13.1*

* $P < 0.05$

A deceased donor liver was available in one pediatric patient with hepatic rejection who underwent successful re-transplantation [8]. One patient with reactivation of hepatitis C is still alive. The other six patients died; their mean survival rate was 28.5 ± 39.8 days (between 3 and 107 days). Three patients who presented multiple organ dysfunction and sepsis at the beginning of MARS procedures deteriorated very rapidly and died in less than a week despite MARS therapy and intensive support care.

Patients with post-hepatectomy liver failure

The first patient was a 57-year-old female who underwent hepatic resection for gallbladder cancer with local invasion. She received one MARS procedure and after spontaneous liver recovery was discharged from hospital. The other patient was a 51-year-old male patient with viral hepatitis B and hepatic cancer who underwent hepatic resection and developed post-hepatectomy liver failure. He received one MARS therapy and presented a transient improvement of clinical and biological parameters.

Discussion

We hereby reported the results of MARS therapy in 27 patients with severe liver failure. The outcome was different depending on the indication for MARS dialysis. We used the international indications for MARS treatment derived from randomized controlled studies, controlled trials or analytic case-control studies [9-16].

The indication for MARS treatment was ALF in 7 cases. The main clinical change observed after the application of MARS therapy was the improvement of HE. However, the patient with grade IV HE did not improve the HE grade and died three days later. The poor result in this case could be related to late intervention. Best results were achieved in the patients with ALF who had been intoxicated with acetaminophen, and in those with hepatitis B infection. There are limited controlled data regarding the effect of MARS therapy in ALF. In 2003, Schmidt et al [17] conducted a prospective, controlled study to assess the effects of a single 6-hour MARS treatment on hemodynamics and oxygen consumption in13 patients with hyperacute liver failure (HALF). They found that MARS treatment increased systemic vascular resistance and arterial blood pressure, decreased cardiac index and heart rate, and improved oxygen consumption in patients with HALF. Survival rate was not different between the MARS patients and controls. Novelli et al [18] treated 16 patients with fulminant hepatic failure: 10 patients underwent orthotopic liver transplantation, 3 died because of sepsis and in 3 cases they obtained complete recovery. They reported significant improvement in the Glasgow Coma Score, serum bilirubin, ammonium, and creatinine.

The benefit of MARS therapy has been more clearly shown in patients with AoCLF complicated with hepatorenal syndrome, severe cholestasis or HE. Mitzner et al [9, 19] evaluated 13 patients with AoCLF associated with type I hepatorenal syndrome, randomized either to MARS (n=8) or standard medical therapy and hemodiafiltration (n=5). The authors reported that at day 7, the mortality rate was 62.5% (75% at day 30) in the MARS group versus 100% in the control group. Heemann et al [10] conducted a prospective, controlled study to evaluate the effects of MARS in 24 patients with cirrhosis and superimposed acute injury with progressive hyperbilirubinemia. At day 30, 11/12 patients in the MARS group were still alive, as compared to 6/11 patients in the control group. Another randomized controlled

study [11, 13] showed that the use of MARS may be associated with an earlier and more frequent improvement of HE in patients with advanced cirrhosis and severe HE. The study however did not prove survival benefit. In our patients with AoCLF treated with MARS we obtained a significant improvement in bilirubin and creatinine levels, but we did not observe much benefit in patients who did not undergo liver transplantation. However, due to MARS therapy, the patients' survival increased with 24.5 ± 34.6 days, which allowed preparation for liver transplantation. Based on our experience, the profile of the patient with AoCLF who will benefit the most from MARS therapy should have no more than two organ failures and no major co-morbidities. In addition, we noticed that patients with high reductions in bilirubin level had a favourable clinical evolution. The main limit of the present study is that, because of the small number of patients included with different etiology of liver failure and different number of MARS sessions applied, we cannot conclude regarding specific protocols for MARS therapy and prognosis according to the liver failure aetiology.

Current literature shows limited experience regarding the use of MARS therapy in graft dysfunction following liver transplantation and post-hepatectomy liver failure [12, 20]. Our study included 8 patients with post-transplantation liver failure and 2 patients with post-hepatectomy liver failure. In the post-transplantation liver failure group, MARS therapy was followed by a significant improvement in total bilirubin, creatinine, lactate, sodium and mean arterial pressure. However, the poor survival results were related to the presence of multiple organ dysfunction and sepsis in many patients.

Due to the low availability of deceased donor liver transplants and living donor liver transplants, many of the studied patients did not undergo liver transplantation. The long-term outcome of severe liver failure patients depends on the availability of liver transplantation or own liver recovery. Methods to bridge the period of acute decompensation until recompensation or until transplantation or liver regeneration and complete recovery are required. A recent observational cohort study conducted by Camus et al [21] assessed the usefulness of MARS dialysis in patients with ALF who fulfill criteria for liver transplantation. The authors observed a statistically significant improvement of liver function after MARS therapy and concluded that MARS albumin dialysis could be safely used as an adjunctive therapy in patients with ALF of medical causes. A meta-analysis suggested that artificial liver support reduced mortality in AoCLF but not in ALF [22]. Another systematic review on MARS for ALF and AoCLF showed that MARS treatment had no significant survival benefit on patients with liver failure when compared to standard medical therapy [23].

In **conclusion**, MARS therapy is an efficient therapy for the removal of water soluble and albumin-bound toxins in acute liver failure, post-transplant liver insufficiency, acute on chronic and post-hepatectomy liver failure. However, hepatic synthesis function did not change after treatment and this is one of the main limitations of the method. The unfavorable prognosis factors were the association with multiorgan failure and sepsis.

Conflicts of interest

There is no conflict of interest regarding our study.

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