Molecular Adsorbent Recirculating System for Acute and Acute-on-Chronic Liver Failure: A Meta-analysis

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Molecular adsorbent recirculating system (MARS) is an important option for patients with liver failure to give them additional time for recovery or to serve as a “bridge” to transplantation. However, its effect on survival for such patients is not well known. Our aim was to assess the treatment effects of MARS on patients with acute and acute-on-chronic liver failure. The outcomes measure evaluated was survival. We searched Medline (1966–2002) and EMBASE (1974–2002) using the terms liver failure, liver support systems, and MARS. Our search was extended to the Cochrane Controlled Trials Registry Database, published abstracts from 5 international conferences, Teraklin (the manufacturer of MARS), known contacts, and bibliographies from each full-published report. We included trials published in English and non-English languages. Eligible studies were randomized and nonrandomized controlled trials, which compared the treatment effects of MARS with standard medical treatment. Of the 206 articles screened, 4 randomized controlled trials including 67 patients were analyzed. Two nonrandomized trials with 61 patients were used for exploratory analysis. The methodology, population, intervention, and outcomes of each selected trial were evaluated by duplicate independent review. Disagreements were resolved by consensus. In the primary meta-analysis, MARS treatment did not appear to reduce mortality significantly compared with standard medical treatment [relative risk (RR), 0.56; 95% confidence interval (CI), 0.28–1.14; P = .11]. Only 1 of the 4 randomized trials analyzed showed significant reduction in mortality. Sensitivity analysis of 3 peer-reviewed trials did not reduce mortality significantly with MARS treatment (RR, 0.72; 95% CI, 0.37–1.40; P = .33). Subgroup analysis of 2 trials for acute liver failure and another 2 trials for acute-on-chronic liver failure also did not reveal any benefit to survival with MARS treatment. In contrast, explorative analysis of 2 nonrandomized trials showed a significant survival benefit with MARS treatment (RR, 0.36; 95% CI, 0.17–0.76; P = .007). This was possibly related to bias in the selection of patients in the nonrandomized trials. In conclusion, MARS treatment had no significant survival benefit on patients with liver failure when compared with standard medical therapy. However, we found only a few trials with a small number of patients for the analysis, allowing for the possibility of false negative and erroneous conclusions. Well-conducted randomized trials are strongly recommended to define the role of MARS in the treatment of patients with liver failure. (Liver Transpl 2004;10:1099–1106)

Liver failure is characterized by the development of hepatic encephalopathy, jaundice, and coagulopathy. The disorder may rapidly progress to multiorgan failure and death. It is broadly divided into 2 syndromes: acute liver failure (ALF) and acute-on-chronic liver failure (AOCLF). ALF is defined as the onset of coagulopathy and encephalopathy within 8 weeks of symptom presentation in an individual with no known underlying liver disease.1,2 Emergency liver transplantation continues to offer the only chance of survival for patients with ALF.3,4 Liver transplant should be offered early enough in such patients before severe, irreversible brain damage has ensued. The selection of patients, appropriate timing of the transplant, shortfall of organs, difficulty of making donor livers available within a short period of time, and postoperative course of these sick patients make the transplantation for ALF patients a very challenging field. Thus, a large number of patients still die waiting for a donor organ to become available.

AOCLF refers to an acute deterioration in liver function in a patient with previously well-compensated chronic liver disease caused by the effects of a precipitating event such as sepsis or upper gastrointestinal bleeding.5 The entity has high mortality caused by multiorgan failure. The most noticeable clinical manifestations of AOCLF include hepatorenal syndrome and hepatic encephalopathy. Management is focused at supportive therapy aimed at the failing organs in the hope that the liver will recover if the patient can be supported through this acute deterioration.

Abbreviations: ALF, acute liver failure; AOCLF, acute-on-chronic liver failure; MARS, molecular adsorbent recirculating system; RR, relative risk; CI, confidence interval.

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Both ALF and AOCLF need a liver support system either to give additional time for recovery of the liver to occur or to serve as a “bridge” to transplant.6–10 Broadly, 2 types of systems have been developed. In bioartificial systems, the aim is to provide all the functions of the normal liver cells with either human hepatic cells as in the extracorporeal liver-assisted device (ELAD; Vitgen Inc, La Jolla, CA) or porcine hepatocytes (the HepatAssist device, Circe Biomedical, Lexington, MA). Artificial liver support systems are based on the provision of detoxification functions using only membranes and adsorbents, which can remove the putative toxins associated with liver failure. These include systems with whole blood exchange, charcoal hemoperfusion, plasma exchange with hemoperfusion, and hemodialbsorption with powdered-activate charcoal (the BioLogic-DT, Hemotherapies, San Diego, CA). However, the molecular adsorbent recirculating system (MARS, Teraklin, AG, Rostock, Germany), which is based on hemodiabsorption with albumin, has caught much attention.11,12 The effect of MARS treatment on survival of patients of ALF and AOCLF is not well known.

We performed a systematic review to evaluate the effect of MARS treatment for patients with ALF and AOCLF.

Methods

Protocol

We sought to conduct a meta-analysis to identify the effect of MARS treatment for patients with ALF and AOCLF. A protocol was written that specified several aspects of the meta-analysis per defined guidelines.13 A checklist was developed for the purpose of data entry.

Acquisition of Data

Medline (National Library of Medicine, Bethesda, MD) and EMBASE (Elsevier, New York, NY) were searched from 1966 to November 2003 to locate published research in the area of liver failure and liver support systems. Medical subject headings (MeSH) terms used for key and text word searching included liver failure, liver-assisted device, and MARS. We also searched the Cochrane Registry of controlled trials database. Published abstracts corresponding to the American Association for the Study of Liver Disease, the American Gastroenterology Association, and the American College of Gastroenterology, United European Gastroenterology Week meetings; the British Society of Gastroenterology; and the International symposia on MARS therapy in liver disease were reviewed also. Teraklin AG Rostock Germany, the manufacturer of MARS; and known contacts in the area of this research were approached. Finally, a manual search was performed using bibliographies from each full-published report.

Study Selection

Criteria for selection.

The following selection criteria were applied:

1. Study design: randomized and nonrandomized controlled trials
2. Language of publication: both English and other languages
3. Study population: patients with ALF or AOCLF
4. Intervention (treatment group): molecular adsorbent recirculating system
5. Comparison intervention (control group): standard medical treatment

Reporting of duplicated studies was excluded by examining the author list, parent institution, sample size, and results.

Outcome measures.

In the protocol, we envisaged using the following outcome measures to assess the effects of MARS treatment in the selected trials:

1. All-cause-deaths within 30 days of randomization
2. Bridge-to-transplantation
3. Effect on hepatic encephalopathy
4. Adverse events

However, we were able to perform meta-analysis on all-cause-deaths only (see the results section). All analyses were performed according to the intention-to-treat method.

Three investigators (MSK, MSK, and KLCF) independently evaluated trials for inclusion and for outcome measures. Any disagreement was resolved by discussion.

Assessment of Study Quality

Two reviewers (MSK and KLCF) independently assessed trial quality by examining the allocation sequence generation and allocation concealment.14,15 The allocation sequence was classified as adequate if based on computer-generated random numbers, table of random numbers, or similar. The allocation concealment was classified as adequate if the allocation sequence was concealed until the moment of randomization by a central independent unit, sealed envelopes, or similar.

Quantitative Analysis

Three of us (MSK, MSK, and KLCF) independently read each reference for quantitative analysis and completed a checklist of questions. The quantitative data abstracted included type of liver failure (ALF and AOCLF), mean age, proportion of men, setting, duration of follow-up, and losses to follow up. Attempts were made to get additional information on missing or ambiguous data from the
investigators. Discrepancies of analysis were resolved by consensus.

Data Analysis

The measure of association used in this meta-analysis was relative risk (RR) with 95% confidence interval (95% CI). Summary RR with 95% CI was calculated using random effect model. A statistically significant result was assumed when the 95% CI did not include 1. Statistical heterogeneity between trials was evaluated by the Cochran Q-2 test and was considered to exist when $P$ less than .1. Where heterogeneity was detected, accepted methods of exploration of statistical heterogeneity using clinical parameters were used. When the RR for an outcome was significant, the number needed to treat to either benefit or harm 1 additional patient with 95% CI was calculated for that measure.

Publication bias was investigated through visual inspection of funnel plots whereby risk ratios were plotted against sample size. Because graphic evaluation can be subjective, a rank correlation test for publication bias was used.

We performed sensitivity analysis to assess the stability of conclusions to assumptions about the probabilities that were used in the analysis and that were done as an assessment of the methodology. For this purpose, we assessed whether type of publication could influence the results of our meta-analysis. Next we performed subgroup analysis to delineate differences in the effects of intervention that were biologically based. For this we performed meta-analyses on patients with AOCLF and ALF separately.

All analyses and calculations were performed using a program (easyMA) developed by the Department of Clinical Pharmacology of the University hospital in Lyon, France.

Results

Literature Search

We identified 206 articles for review (Fig. 1). Six trials met criteria for inclusion. Of the 4 randomized trials, 3 had been published as full manuscripts in peer-reviewed journals and 1 was published only in an abstract form. These trials formed the basis of primary analyses. Another 2 nonrandomized trials were published as full manuscripts in peer-reviewed journals and formed the basis of explorative analysis. There was unanimity between the authors about the selection of relevant articles.

Study Design and Patient Characteristics

The 4 randomized trials included 67 patients; 36 (53.7%) had received MARS treatment, and 31 (46.3%) had received standard medical treatment (Table 1). Of these, 2 trials included 37 patients with AOCLF. In 1 of these trials, patients of AOCLF with type 1 hepatorenal syndrome were included. In addition, these patients had serum bilirubin greater than 15 mg/dL. In another trial, patients with bilirubin greater than 20 mg/dL were included. The etiology of hepatic cirrhosis in these patients was alcohol in 26, hepatitis viruses in 5, drugs in 2, Budd Chiari syndrome in 1, and biliary cirrhosis in 3. Another 2 trials included 30 patients with ALF. The etiology of ALF was acetaminophen in 10 patients, cardiogenic shock in 17, and hepatitis B in 2, and disulfiram in 1 patient. All trials used MARS plus standard medical treatment in the treatment arm and standard medical treatment in the control arm. MARS was performed for 6 to 8 hours per treatment session and done on a daily basis until a defined end point was reached. Hemodiafiltration was used in the treatment and control arms in trial including patients with type 1 hepatorenal syndrome.

All-Cause-Deaths

All trials reported all-cause-deaths (Fig. 2). Data on bridge-to-transplantation and effect on hepatic encephalopathy were reported in 1 trial each only. The registration of adverse events associated with standard medical therapy was incomplete in all except 1 trial. Thus, we were able to perform meta-analysis on all-cause-deaths only.

Of the 4 trials, only 1 trial published in abstract form showed a significant reduction in the mortality with MARS treatment compared with standard medical treatment (RR, 0.28; 95% CI, 0.08–0.95). The other 3 trials published in peer-reviewed journals did not show any survival benefit. The control group mortality was 67.7% (21/31). MARS treatment did not appear to reduce mortality significantly (33.3%; 12/36) compared with standard medical treatment (RR, 0.56; 95% CI, 0.28–1.14; $P$ = .17). The Cochran Q for heterogeneity for treatment effect was not significant ($P$ = .39), suggesting that the trials for this end point were homogeneous. Inspection of the funnel plots revealed no publication bias ($P$ = .17).

Sensitivity and Subgroup Analysis (Table 2)

We performed post hoc sensitivity analysis by limiting meta-analysis to 3 trials published in peer-reviewed journals. The control group mortality was 59% (13/22). MARS treatment did not appear to reduce mortality significantly (35.7%; 10/28) compared with the standard medical treatment (RR, 0.72; 95% CI, 0.37–1.40; $P$ = .33). The next subgroup analysis was done to determine the treatment effect of MARS on AOCLF and ALF. For this we performed meta-analysis on 2 trials...
including patients with AOCLF (RR, 0.50; 95% CI, 0.12–2.17; \( P = .35 \)) and another 2 trials including patients with ALF (RR, 0.50; 95% CI, 0.15–1.58; \( P = 0.23 \)) separately. In both these analyses MARS treatment did not appear to reduce mortality significantly compared with the standard medical treatment. However, Cochran \( Q \) for heterogeneity of these analyses (sensitivity and subgroup) suggested that trials were homogeneous, and inspection of the funnel plots revealed no publication bias with \( P \) value for rank test nonsignificant.

**Adverse Events**

The registration of adverse events associated with standard medical treatment was incomplete in all except one trial.\(^{22}\) In this study, 91 MARS treatment sessions...
Discussion

This review of 4 randomized and 2 nonrandomized trials compared the effect of MARS therapy with standard medical treatment for severe liver failure. In the primary meta-analysis, as well as sensitivity and subgroup analyses, no significant reduction in mortality was observed in the MARS group compared with the standard medical treatment group. Several issues need to be considered when critically assessing these data.

MARS was introduced by investigators at the University of Rostock, Germany, in 1993, and extensive studies on biochemical and hemodynamic effects of this form of dialysis on patients with acute-on-chronic liver failure (AOCLF) and acute liver failure (ALF) of different etiologies have been performed.11,12,26,27

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Publication</th>
<th>Randomization</th>
<th>Allocation</th>
<th>Study Group</th>
<th>Sample Size (Intervention/Control)</th>
<th>Active Treatment (Number of Sessions Per Patient)</th>
<th>Control Treatment</th>
<th>Primary End Point</th>
</tr>
</thead>
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<tr>
<td>Mitzner 2001#</td>
<td>Randomized</td>
<td>Peer review</td>
<td>Central</td>
<td>Sealed envelope</td>
<td>AOCLF (HRS type 1)</td>
<td>8/5</td>
<td>MARS (5.2*) + HDF + SMT</td>
<td>HDF + SMT</td>
<td>30 day deaths</td>
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<td>Heemann 2002#</td>
<td>Randomized</td>
<td>Peer review</td>
<td>Central</td>
<td>Sealed envelope</td>
<td>AOCLF</td>
<td>12/12</td>
<td>MARS (7.7*) SMT</td>
<td>SMT</td>
<td>Survival</td>
</tr>
<tr>
<td>El-Banayosy 2003#</td>
<td>Randomized</td>
<td>Peer review</td>
<td>Sequential</td>
<td>Sealed envelope</td>
<td>ALF</td>
<td>8/9</td>
<td>MARS (3q) + SMT</td>
<td>SMT + Temperature matched</td>
<td>Heomodynamics</td>
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<tr>
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<td>Randomized</td>
<td>Peer review</td>
<td>Central</td>
<td>Sealed envelope</td>
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<td>8/5</td>
<td>MARS (1) + SMT</td>
<td>SMT</td>
<td>Survival</td>
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<tr>
<td>Hessel 2003§</td>
<td>Nonrandomized</td>
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<td>Central</td>
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<td>8/3</td>
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<td>SMT</td>
<td>1 year survival</td>
</tr>
<tr>
<td>Chen 2002§</td>
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<td>Peer review</td>
<td>Central</td>
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<td>ALF</td>
<td>13/12</td>
<td>MARS (2.7) + SMT</td>
<td>SMT + Temperature matched</td>
<td>Bilirubin levels</td>
</tr>
</tbody>
</table>

Abbreviations: SMT, standard medical treatment; HDF, hemodiafiltration; AOCLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; ALF, acute liver failure; HBV, chronic hepatitis B.

Notes. #studies used for meta-analysis, §studies used for explorative analysis, *maximum MARS sessions allowed were 10 per patient, †MARS sessions were stopped when serum bilirubin was less than 15 mg/dL for 3 consecutive days, maximum of 10 sessions were allowed per patient, ‡initial MARS was performed on 3 consecutive days and continued if serum bilirubin was still > 6 mg/dL. acontrol subjects received MARS session.
Large pools of data based on case reports and case series showing beneficial effect of this therapy on liver failure have been published. Some of these data submitted to the International MARS Registry were published in 2002\textsuperscript{28} and updated recently.\textsuperscript{29,30} Up until now, 385 patients with liver failure treated by MARS have been analyzed. Survivals of more than 55\% in patients with AOCLF and ALF have been reported. No serious side effects related to MARS were submitted to the registry. On this basis, MARS has been recommended for treatment of AOCLF and ALF caused by a wide range of causes. The question remains whether the data available have a sufficient evidence base to recommend MARS in liver failure. Data based on case reports and case series are fraught with bias of multiple types, including the inclusion of selected cases, unblinded assessment of end points, results reported from only positive trials, and conflict of interest in the investigators. These statistical problems can be examined carefully only in well-designed, controlled randomized trials and the level of evidence made more exact on recommendations of MARS in liver failure.

Table 2. Results of Primary Meta-Analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events / Patients</th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>P Value Heterogeneity</th>
<th>P Value Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td></td>
<td>0.56 (^0.28–1.14)</td>
<td>0.11</td>
<td>0.39</td>
<td>0.17</td>
</tr>
<tr>
<td>Sensitivity analysis#</td>
<td></td>
<td>0.72 (0.37–1.40)</td>
<td>0.33</td>
<td>0.33</td>
<td>0.11</td>
</tr>
<tr>
<td>AOCLF§</td>
<td></td>
<td>0.49 (0.12–2.17)</td>
<td>0.35</td>
<td>0.32</td>
<td>0.17</td>
</tr>
<tr>
<td>ALFη</td>
<td></td>
<td>0.49 (0.15–1.58)</td>
<td>0.23</td>
<td>0.32</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Notes. #, analysis done on 3 trials, trial by El-Banayosy et al. 2003 published as abstract was excluded. §, analysis done on 2 trials by Mitzner et al. 2001 and Heeman et al. 2002. η, analysis done on 2 trials by El-Banayosy et al. 2003 and Schmidt et al. 2003.
This study found 4 controlled randomized trials on MARS in patients with AOCLF and ALF. All these trials included a small number of patients; in none of the trials were attempts made to have a sample size calculation performed before initiation of the trial. Because of the nature of therapy, adequate double blinding of patients and caregivers was impossible. Three of these 4 trials reported a significant benefit of MARS treatment on survival compared with standard medical treatment; however, on reanalysis of the data, we failed to confirm this significant beneficial survival effect in 2 of the 3 trials. In fact, there was no survival benefit with MARS even in cumulative summary of RR. Although no significant survival benefit with MARS was found, there was a 44% reduction in mortality on MARS treatment in patients with liver failure. Thus, the conclusion of this meta-analysis that MARS treatment does not benefit patients with ALF or AOCLF must be viewed with caution and may be erroneous. Because the number of patients included in the trials was very few, meta-analysis may not give significant values to the substantial reduction in mortality in the intervention group. This analysis had less than 40% power to detect a 10% reduction in mortality, making the possibility of false-negative conclusions a possibility. This issue can be resolved only by carefully conducted controlled randomized clinical trials including a larger number of patients to give at least 80% power at a 5% significance level to detect differences in the intervention and control group. Such randomized trials need sample size calculations for obtaining proper statistical power. Multicenter trials on MARS in AOCLF and ALF are ongoing, but we were unable to obtain any information on their results at the time of this meta-analysis.

A meta-analysis on liver support systems in patients with liver failure was published recently.10 This study analyzed 7 types of support systems (5 artificial and 2 bioartificial systems) in 12 trials involving 483 patients. In the primary meta-analysis, support systems did not appear to affect mortality (RR, 0.86; 95% CI, 0.65 – 1.12). However, in subgroup analysis, support systems significantly reduced mortality in AOCLF and not in patients with ALF. Two studies on MARS were included in this meta-analysis.20, 21 The problem with this meta-analysis is that a wide range of support systems with different mechanisms of action were analyzed, and this may not give a clear answer to the use of support systems in liver failure. However, in this meta-analysis, the authors concluded that additional randomized trials were needed before support systems could be recommended for routine use.

In the explorative meta-analysis on 2 trials involving 61 patients, we found a significant survival benefit with MARS treatment. This may be because of 2 reasons: (1) all patients in these trials were patients with AOCLF and no patients with ALF were included, and (2) there was bias in the study caused by inclusion of retrospective controls in one study and drop outs of MARS in another study. Similar observations were made in the meta-analysis on liver support systems in liver failure.10 Also, there is evidence that nonrandomized trials have considerable risk of generating false-positive results.31

**Limitations**

This review has potential limitations. The major problem was the small number of patients in either arm, making the possibility of false-negative conclusions. None of the studies reported sample size calculations. Thus negative or false-positive conclusions could occur in these studies because of random error. Meta-analyses are by nature observational and may be affected by bias or confounding. However, the studies included in this analysis were homogenous, and the sensitivity analysis revealed stability of conclusions.

**References**


