Review Article

Molecular Adsorbent Recirculating System (MARS)

HK Tan,[1] *FAMS, MBBS, MRCP (UK)*

Abstract

Introduction: Molecular adsorbent recirculating system (MARS) for albumin liver dialysis has been used as a bridge to liver transplantation in patients with fulminant hepatic failure (FHF). This review examines the available data on its clinical use, its technical aspects and present gaps in knowledge. Methods: Peer-reviewed journals and monographs on the subject were covered. Results: FHF is associated with elevation in various substances including bilirubin, ammonia, lactate, free fatty acids and aromatic amino acids. Some of these toxic metabolites, such as ammonia and bilirubin, are believed to be central to the clinical manifestations of hepatic encephalopathy and acute renal failure. MARS ameliorates both biochemical and clinical manifestations of FHF by removing both water-soluble and protein-bound toxins. Among the benefits of MARS is the attenuation of severe cerebral oedema and raised intracranial pressure found in FHF, possibly through reduction in high concentrations of these toxins. Although MARS has been shown to be useful in FHF, its clinical efficacy in subfulminant hepatic failure and less severe forms of acute liver failure (ALF) remains uncertain. The current literature also suggests that it may be beneficial to treat cases of acute-on-chronic liver failure (AoCLF). Deranged systemic chemistries can be similarly ameliorated, but the impact of MARS on the natural history of AoCLF remains uncertain. The difficulty lies in being able to accurately quantify residual liver function and variability in the course of acute intercurrent events. The broader question is whether MARS can favourably change the natural history of ALF and FHF. For this, large multi-centre, randomised controlled trials are needed. Furthermore, it is also uncertain how hepatic excretory-assist devices, such as MARS, compare with bio-artificial liver-assist devices which have both synthetic and excretory hepatic functions in ALF treatment in intensive care unit patients. Nevertheless, MARS has proven to be a valuable homeostatic tool that may be useful in restoring the biochemical and clinical status quo in much the same way that continuous veno-venous haemofiltration and mechanical ventilation provide temporary artificial organ support while these organs are in distress. This is the evolving concept of multi-organ support therapy. Other major unresolved issues with MARS include the timing of initiation of albumin liver dialysis, the clinical and/or biochemical parameters to base this decision on, the intensity of MARS therapy (continuous versus intermittent) and the saturation capacity of the system for different metabolites in intermittent MARS. Conclusions: MARS is an effective and, thus far, safe homeostatic tool in treating FHF. More studies are needed to delineate its role as a homeostatic tool in less severe forms of ALF, including that which occurs in multi-organ failure and in AoCLF. Other studies need to focus on the optimal timing of initiation of and intensity of MARS albumin liver dialysis. The larger issue is to compare MARS with bio-assist liver devices in treating the whole spectrum of ALF.

Ann Acad Med Singapore 2004;33:329-35

Key words: Acute liver failure, Artificial liver, Dialysis

Introduction

Liver failure is clinically heterogeneous in aetiology, pathophysiology, clinical severity and prognoses.[1-3] It can be divided into the following categories: acute liver failure (ALF), of which the most severe form is fulminant hepatic failure (FHF); acute-on-chronic liver failure (AoCLF), such as acute viral hepatitis flare in those with chronic viral hepatitis or in cirrhotic patients developing liver failure following extensive liver resection for liver cancer; and end-stage liver disease. The last will not be discussed in this article. The causes of ALF include viral hepatitis B, paracetamol overdose[4-6] and toxins such as that from the

[1] Consultant
Department of Renal Medicine
Singapore General Hospital, Singapore
Address for Reprints: Dr Tan Han Khim, Department of Renal Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: hankhim@lycos.com

amanita mushrooms.[7,8] Multiple medical complications and multi-organ failure (MOF) can result from severe ALF.[9] These include acute renal and respiratory failure, severe sepsis, bleeding diatheses, disseminated intravascular coagulation, acute encephalopathy and significant haemodynamic derangements. Conditions such as severe sepsis can cause secondary ALF of variable severity. Mortality in patients with severe ALF remain high, ranging from 40% to 80%.[9,10] In the absence of contraindications, liver transplantation is the treatment of choice in irreversible FHF; nevertheless its use is limited by organ donor shortage, especially in countries like Singapore where the supply of livers suitable for transplantation is limited and unpredictable.[10-12] An integral strategy is to optimise patients' medical condition, either in anticipation of liver transplantation in FHF patients or of spontaneous liver recovery. Good care in the intensive care unit (ICU) remains the cornerstone of medical treatment for such patients.[13] This is complemented by the use of extracorporeal liver assist devices (ELADs), which provide acute temporary liver support to further optimise the internal milieu in these patients.

Generally, ELADs can be divided into the following categories:[14] biological devices using whole animal livers; hybrid bio-artificial devices using immortalised hepatocytes cultured in bio-reactors that provide both excretory and synthetic liver functions mimicking endogenous hepatic function; combinations of both; and non-biological ELADs having no synthetic functions, relying instead on extracorporeal blood purification to substitute for failed or inadequate endogenous hepatic excretory function. Bio-artificial livers will not be discussed further.

Extracorporeal blood detoxification, as a means of substituting for severely impaired or failed endogenous liver excretory function, has been explored using charcoal sorbent in a technique known as charcoal haemodiadsorption.[15] This Liver Dialysis System, previously termed the BioLogic Push-Pull Sorbent System (Hemocleanse Inc, W. Lafayette, IN, USA), was shown to be effective in treating hepatic encephalopathy (HE) in cases of acetaminophen-induced ALF.[16] Another ELAD for blood purification is the molecular adsorbent recirculating system (MARS; Teraklin AG, Rostock, Germany).[17] It utilises albumin as a molecular adsorbent to remove albumin-bound liver toxins from the patients' blood compartment. These substances include ammonia, bilirubin, free fatty acids and aromatic amino acids.[17] Some of these have been shown to play an important role in the pathogenesis of ALF, in particular, extrahepatic organ dysfunction such as acute renal failure (ARF) and HE.[18-21] Available data strongly suggests that improvements in the clinical parameters of cerebral function, such as cerebral blood flow velocity and intracranial pressure (ICP) following MARS treatment, may be due to the removal of mediators like ammonia and other protein-bound liver toxins.[22] However, this has not been confirmed directly. Indirect data have come from the use of therapeutic plasma exchange in treating paediatric ALF, which was shown to improve bleeding diatheses, but not neurological status.[23] A possible explanation is that unlike MARS, therapeutic plasma exchange does not eliminate protein-bound toxins. Such protein-bound toxins may be more critical to the pathogenesis of cerebral dysfunction in ALF.

The present review examines the laboratory and clinical data on albumin liver dialysis with MARS. The technical and operational aspects of MARS therapy are also described. Finally, gaps in our knowledge of MARS will be highlighted to form the basis for future work on MARS and in the broader field of advancing the technique of acute liver replacement therapy using ELADs.

Pathophysiology of Acute Liver Failure

The severity of ALF spans a continuum and clinical outcome is variable. Moreover, many of the clinical and laboratory manifestations of liver failure are non-specific. Primary ALF resulting from direct liver insults, if severe enough, can result in extrahepatic complications such as ARF and bleeding diatheses. Systemic conditions, such as severe sepsis and cardiogenic shock, may cause secondary liver failure and MOF as part of the critical illness complex.[24] The severity of ALF developing after certain insults may be mild to moderate. Acute drug-induced (either idiosyncratic in nature or through overdose) and viral hepatitis are possible additional causes. The course of mild-to-moderate ALF is generally self-limiting. Severe ALF may be subdivided into FHF and subfulminant hepatic failure (sFHF). FHF is defined as the onset of severe ALF complicated by the onset of HE <2 weeks after the onset of jaundice, whereas sFHF is defined as the onset of clinical HE between 2 weeks to 3 months after the development of jaundice, based on the definitions by Bernuau and Benhamou.[24] Thus, FHF represents the most lethal form of severe ALF, in which the likelihood of spontaneous liver recovery is low. FHF complicated by ARF is associated with almost 100% mortality.[24] The aetiology of FHF may be divided into 4 major categories: infective (acute viral hepatitis A [HAV], viral hepatitis B [HBV] and hepatitis C [HCV]), drugs/toxins/chemicals such as halothane, acetaminophen, isoniazid and amanita phalloides, cardiovascular such as portal vein thrombosis, cardiac tamponade and circulatory shock, and metabolic such as Wilson's disease, Reye's syndrome and acute fatty liver of pregnancy.[25] FHF is itself associated with multiple extrahepatic complications, some of which have been alluded to earlier.

Two major complications of FHF are ARF and severe

cerebral oedema. Severe cerebral oedema is a major and often fatal complication in FHF patients. It causes intracranial hypertension leading to cerebral ischaemia and herniation.[26] ARF, as a complication of FHF, is associated with a poor outcome and may require treatment with continuous veno-venous haemofiltration (CVVH).[27] Other complications of FHF include coagulopathy, hypotension, bleeding and malnutrition as a consequence of the hypercatabolic state in these patients.[28]

There are also multiple biochemical abnormalities in FHF. Raised systemic blood concentrations of bilirubin, bile salts, ammonia, lactate, free fatty acids (FFAs), aromatic amino acids, gamma-aminobutyric acid (which is a false neurotransmitter) and mercaptans have all been documented.[29,30] Of these, ammonia is believed to play a central role in the pathogenesis of HE, the so-called ammonia neurotoxicity hypothesis.[31-33] The accumulation of these substances is itself pathogenic in FHF. For example, bilirubin has been shown to be toxic to polymorphonuclear neutrophils, impairing their oxidant killing of bacteria.[34] It is, therefore, logical to expect that reduction in the levels of some of these metabolites and toxins that accumulate in FHF may be beneficial. One way is to detoxify the blood in an extracorporeal circuit. By doing so, the toxic potential of these accumulated metabolites may be reduced. Such a strategy of using a blood purification tool would be adjunctive to conventional care in the ICU. MARS is one such homeostatic tool that can be used for this purpose.

AoCLF, by definition, denotes the presence of chronic liver disease (CLD) prior to the onset of acute liver injury. The pre-existence of CLD may not be known from the outset. The causes of CLD include chronic viral hepatitis, chronic ethanol ingestion, Wilson's disease and cryptogenic cirrhosis. These conditions may only become clinically apparent for the very first time with features of severe ALF following an insult. Acute precipitating factors are variable and may include severe sepsis, gastrointestinal bleeding, ingestion of sedatives and use of hepatotoxic drugs. The manifestations of AoCLF may be similar to those in mild-to-moderate ALF, except that there is no CLD in the latter. Most patients with AoCLF recover spontaneously following resolution of the acute precipitating factor(s). A subset of such patients may progress to sFHF or even FHF.[35] MARS is of use in ameliorating specific biochemical and clinical end-points in AoCLF. It may facilitate recovery from the acute phase of hepatic decompensation.[36] However, it is uncertain whether this significantly impacts on the natural history of the underlying CLD.

Technique

MARS is the device used to perform albumin liver dialysis. The basic technical concept is based on conventional haemodialysis (HD). In HD, blood is pumped through an extracorporeal blood circuit (EC) across a haemodialyser and returned to the patient via a temporary or permanent vascular access. The blood undergoes extracorporeal "cleansing" or dialysis before it returns to the body. Much of the physical set-up and machine design is to maintain the integrity of the EC by the prevention and detection of blood and air leakage from and into the blood circuit. Other HD machine features permit the measurement and display of dialysate conductivity and temperature data, as well as venous pressures and blood flow data. Anticoagulation is used to prevent frequent clotting in the circuit that can potentially reduce the overall dialytic efficiency of HD treatment. Fresh bicarbonate-based dialysate is pumped through the dialysate compartment of the same haemodialyser in a countercurrent direction. By doing so, an adequately steep diffusion gradient is set up for uraemic solutes to diffuse from the blood compartment into the dialysate compartment. Spent dialysate saturated with uraemic solutes is discarded. The dialysate compartment is thus an "open" one, in that fresh dialysate is continuously pumped through the dialyser throughout HD treatment. Conventional HD, therefore, dialyses blood against aqueous bicarbonate dialysate. This permits diffusive clearance of non-protein-bound, water-soluble uraemic solutes, such as urea and creatinine. The corollary is that substances that are tightly protein-bound and present in small quantities in the aqueous phase or are lipophilic would be removed by HD in negligible amounts, if at all.

In contrast, MARS interposes an albumin dialysate circuit in between blood in dialyser 1 and bicarbonate dialysate in dialyser 2 (Fig. 1). The MARS monitor (Teraklin AG, Rostock, Germany) has a single roller pump that pumps albumin round the albumin dialysate path. It must be coupled to either a standard HD machine for intermittent MARS therapy or a continuous renal replacement therapy (CRRT) machine, such as the Prisma (Gambro, Lyon, France), for continuous MARS treatment (Fig. 2). The HD/CRRT machine provides pumps for blood and bicarbonate dialysate circulation in their respective paths in the EC. Blood leaves the patient via a standard dual-lumen, central venous dialysis catheter, such as the 11F Gamcath (Gamcath, Hechingen, Germany). The MARS circuit must be primed 1 to 2 hours ahead of its anticipated use. Upon initiation of MARS therapy, albumin is pumped through the dialysate compartment of dialyser 1, a high flux polysulfone capillary haemodialyser (Fig. 1). Simultaneously, blood enters the hollow fibre lumina of dialyser 1 and is thus bathed in and surrounded by albumin dialysate. This allows for the exchange of protein-bound substances between the blood compartment and albumin in the albumin dialysate compartment. At the same time, water-soluble, non-protein-bound solutes such as uraemic toxins diffuse from the blood into the albumin compartment. Albumin leaving

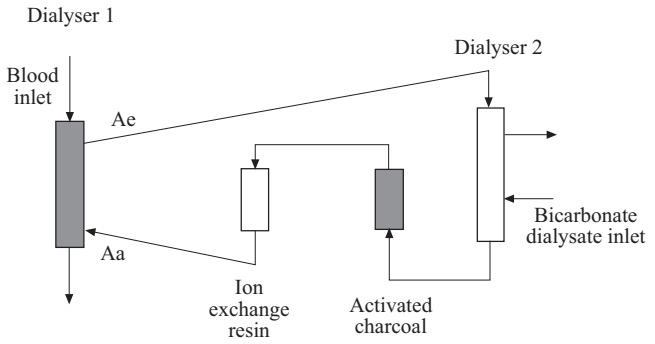

Fig. 1. Diagrammatic representation of a MARS circuit. Aa: albumin dialysate entry into dialyser 1; Ae: albumin dialysate exit from dialyser 1.

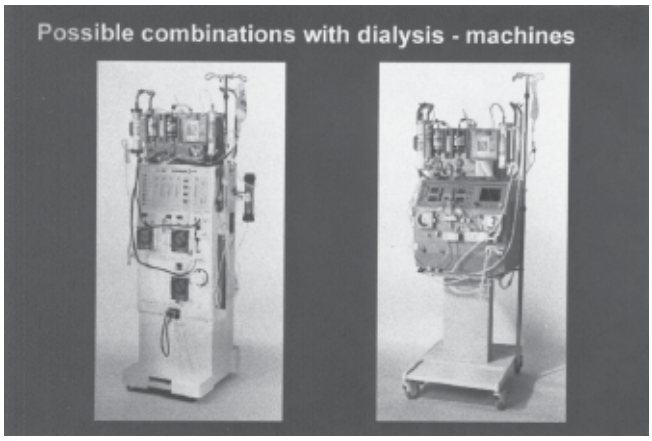

Fig. 2. Photograph of MARS coupled to (a) standard haemodialysis and (b) continuous renal replacement therapy machines.

dialyser 1 is, therefore, saturated with both albumin-bound liver toxins and non-protein-bound aqueous-phase uraemic solutes. This "spent" albumin is then pumped through the "blood" compartment of dialyser 2 (a low-flux polysulfone hollow-fibre dialyser). At the same time, fresh bicarbonate dialysate is pumped continuously by the HD/CRRT machine (with which MARS is coupled) through the dialysate compartment of dialyser 2. Thus, the capillary fibres of dialyser 2 are filled with albumin saturated with liver and uraemic toxins. These albumin-filled hollow fibres in dialyser 2 are, in turn, bathed with fresh bicarbonate dialysate pumped in a direction countercurrent to that of pumped albumin flow through dialyser 2. Thus, uraemic toxins can diffuse from the albumin compartment of dialyser 2 into the bicarbonate dialysate. This explains the de-uraemisation or dialytic effect of MARS in ALF patients with concomitant ARF. Hence, albumin that leaves the "blood" compartment of dialyser 2 has lower concentrations of uraemic toxins than at the point of entry into dialyser 2, but still has a high concentration of liver toxins that have not been removed from albumin dialysate. The second component of the MARS circuit starts with albumin leaving dialyser 2 and entering the activated charcoal column. On exit, albumin enters the anionic exchange column. The passage of albumin through these 2 columns regenerates or "scrubs" it of liver toxins. By the time albumin leaves the anionic exchange resin column and re-enters the dialysate compartment of dialyser 1, it should have a lower concentration of both protein-bound liver toxins and water-soluble uraemic solutes than at Ae. Once more, recycled albumin at Aa is ready to adsorb more liver and uraemic toxins from the blood compartment in dialyser 1. It is clear that while the bicarbonate dialysate compartment is an "open" one with potentially unlimited de-uraemisation capability, the albumin dialysate compartment is "closed" and has an inherent theoretical adsorptive limit, although the time when this is reached and with respect to which substance are currently unknown. A total of 600 mL of 20% albumin is used to prime and fill the albumin dialysate circuit. This amount is neither replaced nor replenished during each session of intermittent MARS treatment. Therefore, the capacity of the albumin dialysate to adsorb protein-bound toxins from the blood compartment is limited by the albumin-regenerating capacity of the charcoal and anionic resin columns. Anticoagulation is needed to maintain a patent blood path in dialyser 1. Different approaches to anticoagulation (regional versus systemic) and different types of anticoagulants have been used in CRRT, although similar experience with MARS is relatively more limited.[37-39] Studies are, therefore, needed to identify the optimal choice of anticoagulant, mode of administration and dosage needed for MARS. In some patients with very high bleeding risk, it may be possible to omit anticoagulation altogether. This has also been proven in CVVH in patients at high bleeding risk and who are already spontaneously coagulopathic and/or thrombocytopaenic.[40]

Prescription of Albumin Liver Dialysis Using MARS

Once it is decided that MARS therapy is to be carried out, a central venous catheter should be inserted as with any CRRT or extracorporeal blood purification procedure. This catheter may be inserted into any of the large central veins: femoral, internal jugular and subclavian veins. Fresh frozen plasma and platelet transfusions may be needed during dialysis catheter insertion since most of these patients are coagulopathic and / or thrombocytopaenic. If the patient is already on CVVH for concomitant ARF, the mode of MARS should preferably be intermittent. It is generally not advisable to have CVVH and MARS (either intermittent or continuous) operate simultaneously. Intermittent MARS can be undertaken when CRRT is temporarily stopped. CVVH can be resumed upon completion of MARS therapy.

The duration of an intermittent MARS is 6 to 8 hours. A single MARS treatment should not exceed 10 hours, given the potential risk of albumin becoming a microbial culture medium with prolonged use in MARS. Unfractionated heparin can be prescribed as an anticoagulant (1000 IU to 2000 IU heparin for priming and 250 IU to 500 IU per hour as necessary to prevent blood circuit clotting). It may be possible to use even lower doses of heparin and alternate-hour anticoagulant administration to further reduce the total dose of anticoagulant administered, especially among the very high-risk bleeders. The blood pump speed (Q_B) can range from 150 mL/min to 200 mL/min and albumin dialysate flow rate (Q_A) can be set between a similar range of 150 mL/min to 200 mL/min, in tandem with Q_B and bicarbonate dialysate flow rate (Q_D) at between 300 mL/min to 500 mL/min. Q_A is dialled into the MARS monitor. The other 2 operational parameters are set in the HD or CRRT machine with which MARS is coupled. Generally, the more haemodynamically unstable the patient is, the lower should be the settings for all 3 variables. Depending on the type of HD or CRRT machine being used, Q_D can potentially be set <300 mL/min. Ultrafiltration (UF) is the volume of plasma water that is removed from the blood compartment during dialysis/haemofiltration and this variable is dialled into the HD/CRRT machine. UF can be zero if the patient is highly unstable haemodynamically and is already on CVVH for ARF treatment. If the patient is extremely fluid-overloaded, MARS can be used to achieve a prescribed UF if clinical conditions permit. This must be weighed against the potential of MARS to aggravate hypotension in such patients. Exacerbation of hypotension in ALF patients may cause further ischaemic damage to the diseased liver and worsen the prognosis of ALF. Thus, prescribing no or minimal UF and the lowest Q_B, Q_A and Q_D deliverable by the HD/CRRT machine are ways to attenuate the destabilising potential of MARS during clinical use. The MARS kit should be discarded after a single use and the HD/CRRT machine decontaminated in accordance with prescribed procedures. There is presently no computational approach to quantify either the dose of liver dialysis prescribed or achieved. Liver dialysis dosing with MARS is empiric. Clinical assessment of its efficacy consists of measuring specific blood chemistries pre- and post-MARS. These can include bilirubin, lactate and ammonia. ICP probes can also provide real-time pre- and post-MARS treatment data on ICP and cerebral perfusion.

MARS in Acute Liver Failure and Acute Decompensation of Chronic Liver Disease

The severity of ALF spans a continuum that can be arbitrarily divided into mild, moderate and severe. FHF is the most severe form of ALF and is associated with a high mortality rate. All forms of ALF have variable natural history, with the less severe forms having a higher chance of recovery generally. However, it can be clinically difficult to determine residual liver function in ALF, the likelihood of spontaneous liver regeneration and the course of ALF, arising either from primary hepatic insults or secondary to MOF. Given such variability, the effect of MARS on the course of ALF can be unpredictable. Spontaneous liver recovery may be due to the natural history of the disease in a particular patient and not due to the effect of MARS. Large prospective, randomised, multi-centre clinical trials are needed to answer this central question. Nevertheless, MARS has been shown to be an effective homeostatic tool in FHF when intermediate biochemical outcomes and clinical parameters are considered. Raised bilirubin, bile acids and ammonia levels can be ameliorated with MARS.[41] Other toxins that have been reported to be removed during MARS include urea and creatinine, and this is the basis of the de-uraemisation effect of MARS in patients with concomitant ALF and ARF.[41-43] MARS has also been used to treat patients with AoCLF.[36] In one study, MARS complementing standard medical therapy (SMT) was shown to be associated with a better 30-day survival, together with a significant reduction in plasma bilirubin and bile acids. In addition, HE and renal dysfunction also improved in the MARS + SMT group compared to the control group which received SMT alone.[36] In an uncontrolled series of 8 cases of AoCLF, MARS reduced systemic concentrations of plasma lactate, ammonia, urea, creatinine and bilirubin. The same study also noted that 3 patients experienced reductions in ICP and jugular bulb oxygen saturation with an increase in the cerebral perfusion pressure.[44] MARS has also been shown to increase cerebral blood flow velocity after a single treatment, although the precise mechanism remains uncertain.[45]

A subset of patients with AoCLF are those with acute hepatorenal syndrome, a severe complication of chronic cirrhosis. A total of 13 patients with cirrhosis were studied, of whom 8 were randomised to the MARS + haemodiafiltration (HDF) + SMT treatment arm and 5 (control group) were assigned HDF + SMT only. None of the patients underwent liver transplantation (LTx) during the study. Significantly, mortality was 100% in the control group. In contrast, patients in the MARS-treated group had a mortality rate of 62.5% on day 7 and 75% on day 30.[46] Patients with ALF following extensive liver resection for tumour are another group that can be treated with MARS. MARS can provide temporary hepatic excretory support in anticipation of spontaneous liver recovery following ablative liver surgery. Its use can also be extended to liver transplant patients with primary graft dysfunction. Data suggests that MARS can bridge such patients to either re-transplantation or till spontaneous liver recovery occurs.[47,48]

Unanswered Questions

MARS is effective in ameliorating biochemical and specific clinical parameters that are deranged in FHF and in certain groups of patients with AoCLF. Together with acute renal replacement therapy and good conventional care in the ICU, MARS can keep these patients alive while waiting for LTx or till liver recovery occurs spontaneously. More data from large multi-centre, randomised controlled trials are needed to further confirm this. Much less certain is the effect of MARS on the course of ALF in the context of MOF and the use of MARS in less severe forms of ALF.

Another issue relates to the optimal timing of initiation of and intensity of MARS treatment. ARF patients treated with renal replacement therapy earlier had better survival compared with those treated later with renal replacement therapy (RRT).[49] Extrapolating this concept to ALF, it may be possible that earlier initiation of MARS is potentially beneficial to FHF patients. MARS can be performed intermittently or continuously. Although the dosing of albumin liver dialysis is still unresolved, it may be more physiological to perform continuous rather than intermittent MARS therapy. However, such an approach would be more costly. A more intensive approach to CVVH in ARF has already been shown to be associated with better patient survival.[50] It may be possible that more intensive approaches to MARS treatment can similarly confer a better outcome on FHF patients. Finally, the clinical and laboratory criteria guiding the initiation, timing and intensity of MARS and for what categories of ALF/AoCLF are still evolving. Most studies have used bilirubin as the marker of choice. Further studies are needed to confirm if bilirubin is patho-physiologically relevant and accurate as one of the criteria upon which decisions about MARS are based. This would be analogous to the use of serum urea and creatinine to guide diagnostic and therapeutic decisions in ARF.

Conclusions

MARS is an effective tool in treating patients with FHF. Together with standard care in the ICU, MARS can keep critically ill patients with FHF alive for LTx, should a suitable organ be available and if the patient remains medically fit for transplantation surgery. MARS has also been shown to be useful in ameliorating the internal milieu in patients with AoCLF and in reducing the high mortality rate in some of them. Large multi-centre, controlled trials are needed to confirm if MARS actually changes the natural history of FHF/AoCLF. Much less is known, however, about the usefulness of MARS in treating less severe forms of ALF, especially those that arise in the context of MOF, and whether it changes the course of underlying CLD in AoCLF. More data is also needed to determine the optimal timing and intensity of MARS therapy in selected patients. Evolving indications of MARS include its use as a temporary liver excretory support device in patients with postoperative ALF following extensive ablative liver surgery for tumour and its use as a bridge to either liver re-transplantation or while awaiting spontaneous liver recovery in those with primary liver graft dysfunction.

REFERENCES

1. Herrera JL. Management of acute liver failure. Dig Dis 1998;16:274-83.
2. Bathgate AJ, Hayes PC. Acute liver failure: complications and current management. Hosp Med 1998;59:195-9.
3. Colquhoun SD, Lipkin C, Connelly CA. The pathophysiology, diagnosis and management of acute hepatic encephalopathy. Adv Intern Med 2001;46:155-76.
4. Teo EK, Ostapowicz G, Hussain M, Lee WM, Fontana RJ, Lok AS. Hepatitis B infection in patients with acute liver failure in the United States. Hepatology 2001;33:972-6.
5. Newsome PN, Bathgate AJ, Henderson NC, MacGilchrist AJ, Plevris JN, Masterton G, et al. Referral patterns and social deprivation in paracetamol-induced liver injury in Scotland. Lancet 2001;358:1612-3.
6. Petrelli E, Balducci M, Pieretti C, Rocchi MB, Clementi M, Manzin A. Lamivudine treatment failure in preventing fatal outcome of de novo severe acute hepatitis B in patients with haematological diseases. J Hepatol 2001;35:823-6.
7. Bosia JD, Borzi S, Cocozzella D, Alvarado Torres R, Fraquelli E, Curciarello JO. Acute liver failure: clinical-epidemiological characteristics [Spanish]. Acta Gastroenterol Latinoam 2001;31:383-6.
8. Gill RQ, Sterling RK. Acute liver failure. J Clin Gastroenterol 2001; 33:191-8.
9. Rahman T, Hodgson H. Clinical management of acute hepatic failure. Intensive Care Med 2001;27:467-76.
10. Stockmann HB, Ijzermans JN. Prospects for the temporary treatment of acute liver failure. Eur J Gastroenterol Hepatol 2002;14:195-203.
11. de Rave S, Tilanus HW, van der Linden J, de Man RA, van der Berg B, Hop WC, et al. The importance of orthotopic liver transplantation in acute hepatic failure. Transpl Int 2002;15:29-33.
12. Hashikura Y, Kawasaki S, Miyagawa S, Terada M, Ikegami T, Nakazawa Y, et al. Recent advance in living donor liver transplantation. World J Surg 2002;26:243-6.
13. Larsen FS, Hansen BA, Blei AT. Intensive care management of patients with acute liver failure with emphasis on systemic hemodynamic instability and cerebral edema: a critical appraisal of pathophysiology. Can J Gastroenterol 2000;14:D105-11.
14. Mitzner SR, Stange J, Peszynski P, Klammt S. Extracorporeal support of the failing liver. Curr Opin Crit Care 2002;8:171-7.
15. Ash SR, Caldwell CA, Singer GG, Lowell JA, Howard TK, Rustgi VK. Treatment of acetaminophen-induced hepatitis and fulminant hepatic failure with extracorporeal sorbent-based devices. Adv Ren Replace Ther 2002;9:42-53.
16. Ash SR. Extracorporeal blood detoxification by sorbents in treatment of hepatic encephalopathy. Adv Ren Replace Ther 2002;9:3-18.
17. Steiner C, Mitzner S. Experiences with MARS liver support therapy in liver failure: analysis of 176 patients of the International MARS Registry. Liver 2002;22:20-5.
18. Larsen FS, Gottstein J, Blei AT. Cerebral hyperemia and nitric oxide synthase in rats with ammonia-induced brain edema. J Hepatol 2001;34:548-54.

19. de Knegt RJ, Groeneweg M, Schalm SW, Hekking-Weijma I. Encephalopathy from acute liver failure and from acute hyperammonemia in the rabbit. A clinical and biochemical study. Liver 1994;14:25-31.
20. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29:648-53.
21. Clemmesen JO, Hoy CE, Kondrup J, Ott P. Splanchnic metabolism of fuel substrates in acute liver failure. J Hepatol 2000;33:941-8.
22. Jalan R, Williams R. Improvement in cerebral perfusion after MARS therapy: further clues about the pathogenesis of hepatic encephalopathy? Liver Transpl 2001;7:713-5.
23. Singer AL, Olthoff KM, Kim H, Rand E, Zamir G, Shaked A. Role of plasmapheresis in the management of acute hepatic failure in children. Ann Surg 2001;234:418-24.
24. Bernuau J, Benhamou JP. Fulminant and subfulminant hepatic faillure. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J, editors. Oxford Textbook of Clinical Hepatology. Vol 2. 1st ed. Oxford:Oxford Univ Press, 1991:923-42.
25. Sussman NL. Fulminant hepatic failure. In: Zakim D, Boyer TD, editors. Hepatology: A Textbook of Liver Disease. Vol 1. 3rd ed. Philadelphia:WB Saunders, 1996:618-50.
26. Jalan R, Olde Damink SW. Hypothermia for the management of intracranial hypertension in acute liver failure. Curr Opin Crit Care 2001;7:257-62.
27. Kierdorf HP, Leue C, Arns S. Lactate- or bicarbonate-buffered solutions in continuous extracorporeal renal replacement therapies. Kidney Int Suppl 1999;72:S32-6.
28. Sher LS, Howard TK, Podesta LG, Rosenthal P, Vierling JM, Villamil F, et al. Liver transplantation. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J, editors. Oxford Textbook of Clinical Hepatology. Vol 2. 1st ed. Oxford:Oxford Univ Press, 1991:1429-49.
29. Gitlin N. Hepatic encephalopathy. In: Zakim D, Boyer TD, editors. Hepatology; A Textbook of Liver Disease. Vol 1. 3rd ed. Philadelphia: WB Saunders, 1996:605-17.
30. Clemmesen JO, Hoy CE, Jeppesen PB, Ott P. Plasma phospholipid fatty acid pattern in severe liver disease. J Hepatol 2000;32:481-7.
31. Butterworth RF. Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. Metab Brain Dis 2001;16:55-65.
32. Michalak A, Chatauret N, Butterworth RF. Evidence for a serotonin transporter deficit in experimental acute liver failure. Neurochem Int 2001;38:163-8.
33. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999;29:648-53.
34. Arai T, Yoshikai Y, Kamiya J, Nagino M, Uesaka K, Yuasa N, et al. Bilirubin impairs bactericidal activity of neutrophils through an antioxidant mechanism in vitro. J Surg Res 2001;96:107-13.
35. Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 2002;20:252-61.
36. Heemann U, Treichel U, Loock J, Philipp T, Gerken G, Malago M, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology 2002;36:949-58.
37. Hofmann RM, Maloney C, Ward DM, Becker BN. A novel method for regional citrate anticoagulation in continuous venovenous hemofiltration (CVVHF). Ren Fail 2002;24:325-35.
38. Hidalgo N, Hynes-Gay P, Hill S, Burry L. Anticoagulation in continuous renal replacement therapy. Dynamics 2001;12:13-7.
39. Vargas Hein O, von Heymann C, Lipps M, Ziemer S, Ronco C, Neumayer HH, et al. Hirudin versus heparin for anticoagulation in continuous renal replacement therapy. Intensive Care Med 2001;27: 673-9.
40. Tan HK, Baldwin I, Bellomo R. Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. Intensive Care Med 2000;26:1652-7.
41. Awad SS, Swaniker F, Magee J, Punch J, Bartlett RH. Results of a phase I trial evaluating a liver support device utilizing albumin dialysis. Surgery 2001;130:354-62.
42. Stange J, Mitzner SR, Risler T, Erley CM, Lauchart W, Goehl H, et al. Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. Artif Organs 1999;23:319-30.
43. Stange J, Mitzner SR, Klammt S, Freytag J, Peszynski P, Loock J, et al. Liver support by extracorporeal blood purification: a clinical observation. Liver Transpl 2000;6:603-13.
44. Sorkine P, Ben Abraham R, Szold O, Biderman P, Kidron A, Merchav H, et al. Role of the molecular adsorbent recycling system (MARS) in the treatment of patients with acute exacerbation of chronic liver failure. Crit Care Med 2001;29:1332-6.
45. Schmidt LE, Svendsen LB, Sorensen VR, Hansen BA, Larsen FS. Cerebral blood flow velocity increases during a single treatment with the molecular adsorbents recirculating system in patients with acute-on-chronic liver failure. Liver Transpl 2001;7:709-12.
46. Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 2000;6:277-86.
47. Kellersmann R, Gassel HJ, Buhler C, Thiede A, Timmermann W. Application of Molecular Adsorbent Recirculating System in patients with severe liver failure after hepatic resection or transplantation: initial single-centre experiences. Liver 2002;22:56-8.
48. Stange J, Hassanein TI, Mehta R, Mitzner SR, Bartlett RH. 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. Artif Organs 2002;26:103-10.
49. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early versus late. Intensive Care Med 1999;25:805-13.
50. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356:26-30.