

The Efficacy of Albumin Dialysis in the Treatment of Severe Cholestatic Drug-Induced Liver Injury

INTRODUCTION: Drug-induced liver injury (DILI) is a significant cause of acute liver injury and can present as cholestatic injury with or without associated hepatitis. Although most patients with DILI recover with supportive care, some can develop severe refractory cholestasis that impairs recovery of hepatic function, with subsequent progression to acute or chronic liver failure. Current pharmacotherapy and extracorporeal therapies such as hemodialysis have limited benefit. Albumin dialysis is an emerging strategy in the extracorporeal treatment of intoxications caused by protein bound drugs and can be used for the removal of albumin bound bilirubin and bile acids.

CASES SERIES: We describe the efficacy of albumin dialysis with the molecular adsorbent recirculating system (MARS) in the successful treatment of five patients with severe cholestatic DILI that was refractory to standard medical therapy. All patients had a sustained improvement in serum bilirubin levels after completing MARS therapy, with a complete resolution of their liver injury.

DISCUSSION: Our case series demonstrates that albumin dialysis could provide an important treatment strategy in the setting of severe refractory cholestatic DILI and be considered as a novel therapeutic option in specific cases of drug hepatotoxicity in which the causative agent has high protein binding characteristics.

KEY WORDS: albumin dialysis; drug-induced cholestasis; drug-induced liver injury; molecular adsorbent recirculating system

Drug-induced liver injury (DILI) accounts for a significant portion of all acute liver injury across the world. In addition, the growing global epidemic of herbal hepatotoxicity has increased the burden of DILI-induced hepatic dysfunction and failure (1). Depending on the agent and mechanism of action, DILI can manifest as a predominantly cholestatic injury and associated jaundice, with or without hepatocellular injury. There have been many advances in elucidating the mechanisms of cholestatic DILI. However, treatment options remain limited and are primarily withdrawal of the offending agent and supportive care (2).

Most patients who develop cholestatic DILI will have resolution of the hepatic abnormalities with cessation of the offending agent over a period of days to months. However, there are instances where the cholestasis is severe enough that it impairs recovery of intrinsic hepatic function, with progression to acute or chronic liver failure. In cases that are characterized by severe cholestasis, the potential benefit of albumin dialysis is appealing since albumin can bind specific toxins, including bilirubin and bile acids. The molecular adsorbent recirculating system (MARS) is an albumin dialysate-based dialysis system (**Fig. 1**)

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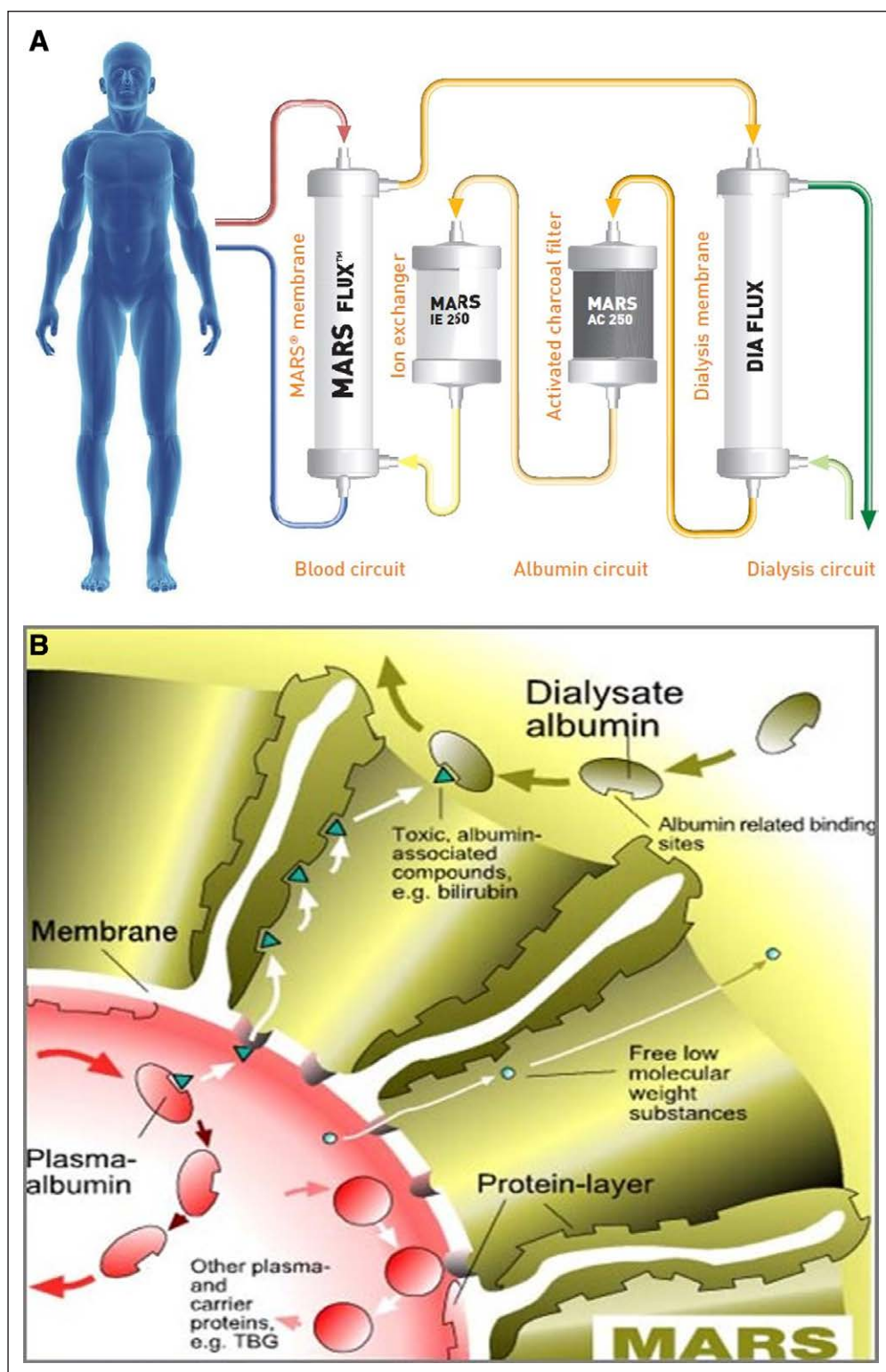


Figure 1. MARS albumin dialysis system. **A**, Details of the molecular adsorbent recirculating system (MARS) circuit, which involves a dialysate of albumin solution that passes through an MARS dialysis membrane and then subsequently via a continuous renal replacement therapy (CRRT) membrane, charcoal filter, and anion exchanger. **B**, Diagram of the MARS membrane, which illustrates the albumin dialysate, and the passage of both water-soluble low-molecular weight as well as larger albumin-bound toxins across the membrane. With kind permission of Baxter. TBG = thyroxine binding globulin.

that facilitates removal of albumin-bound toxins, and there is increasing awareness regarding its application in the extracorporeal treatment of intoxications (3, 4). In a hepatic context, the application of MARS has been associated with improvement in pruritus, jaundice, bile cast nephropathy, and hepatic encephalopathy (5, 6). In this case series, we report our experience using MARS therapy to successfully treat five cases of severe cholestatic DILI that were refractory to standard medical therapy. This study was approved by the Emory University Institutional Review Board (IRB00100506, date of approval: July 12, 2017). Informed consent was waived by our Institutional Review Board given the nature of the study. Procedures were followed in accordance with the ethical standards defined by our Institutional Review Board on human experimentation and by the Helsinki Declaration of 1975.

CASE SERIES

Patients with cholestatic DILI who underwent MARS therapy between 2013 and 2018 were identified using our institutional database. Cholestatic DILI was defined as alkaline phosphatase (ALP) levels greater than two times the

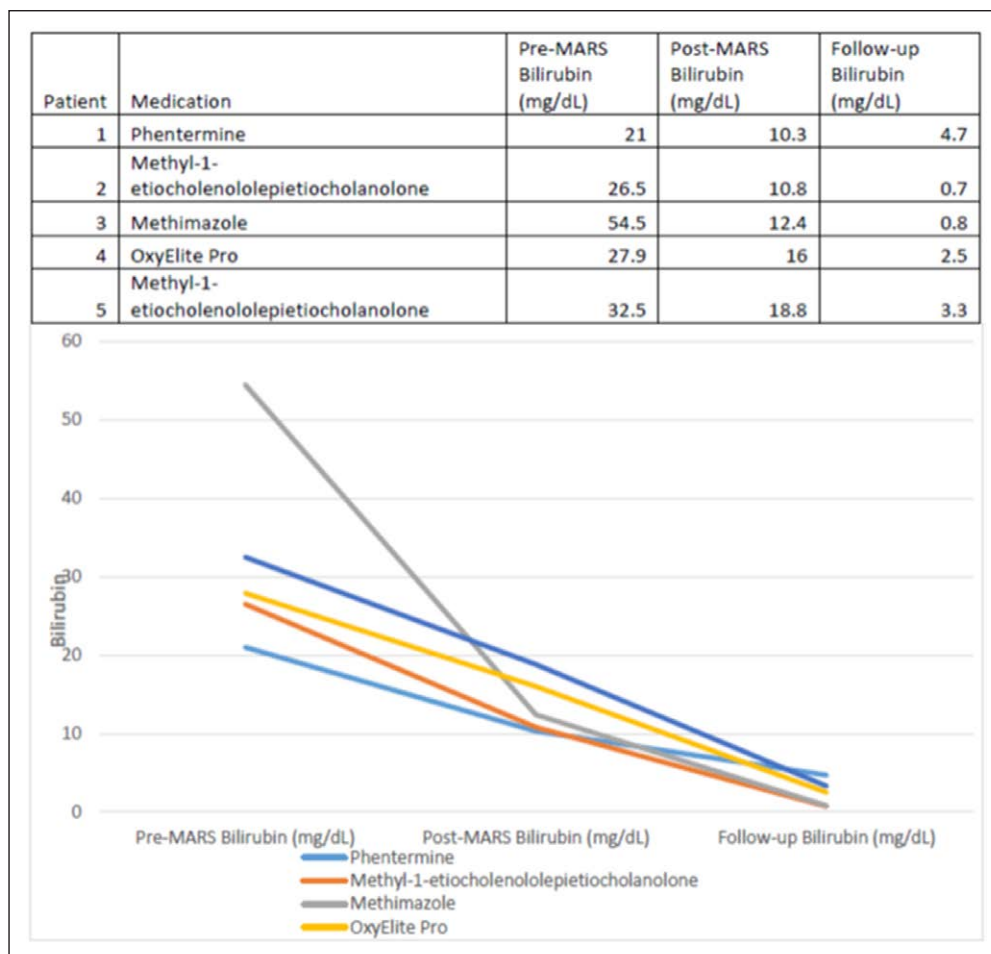


Figure 2. Effect of MARS on drug induced cholestasis. **A**, Table of drugs that caused cholestatic drug-induced liver injury (DILI), with bilirubin noted pre-molecular adsorbent recirculating system (MARS), post-MARS, and at follow-up. **B**, Graph of drugs that caused cholestatic DILI, with bilirubin trends during MARS therapy.

upper limit of normal (>345 U/L) at the time of peak alanine aminotransferase (ALT) or bilirubin elevation secondary to a drug exposure known to cause intrahepatic cholestasis. Five cases of medically refractory severe cholestatic DILI were identified, defined as a persistent serum bilirubin > 20 mg/dL. Hepatotoxic medications included phentermine, methimazole, OxyElite, and two cases of the anabolic steroid methyl-1-etiocholenololepietiocholanolone. In each of the cases, abdominal imaging with MRI was obtained to rule out extrahepatic biliary obstruction and chronic liver disease/portal hypertension, and hemolysis was ruled out with serum biochemical and peripheral smear evaluation. In addition, none of the patients had coexisting critical illness or a systemic infectious trigger that would be risk factors for cholestasis of sepsis. For each of these cases, pre-MARS, post-MARS, and immediate

posthospitalization biochemical data were collected (aspartate aminotransferase [AST], ALT, ALP, Bilirubin, and international normalized ratio [INR]). The dose of MARS therapy was five sessions of albumin dialysis, with each session lasting 8 hours.

Figure 2 summarizes the biochemical data pre and post MARS therapies. Mean total bilirubin prior to MARS was 32.5 mg/dL. Following MARS, patients had significant biochemical improvement, with an average bilirubin of 13.7 mg/dL at the completion of MARS therapy and 2.4 mg/dL at follow-up following inpatient discharge. AST and ALT levels were normal at initial presentation and did not change with MARS therapy. INR levels remained <2 in all cases before and after MARS therapy. None of the patients demonstrated any extrahepatic organ dysfunction, including

hepatic encephalopathy. Sustained improvement in pruritus, jaundice, and overall clinical status was seen in all cases post-MARS. On subsequent outpatient follow-up, all patients had normalization of their clinical and biochemical status, including normalization of their liver enzymes and INR.

DISCUSSION

This cases series highlights the efficacy of the MARS albumin dialysis system in the treatment of medically refractory severe cholestatic DILI. After receiving MARS therapy, all patients had significant improvement in their bilirubin and their symptoms of cholestasis (jaundice and pruritus). In addition, importantly, there was a sustained improvement in the serum bilirubin levels following MARS completion during the inpatient stay and on subsequent outpatient follow-up.

Currently, severe intrahepatic cholestatic DILI as manifested by the patients in this case series has an unfavorable prognosis, with a high risk of progression to subacute liver failure, or chronic fibrosis and cirrhosis. In addition to the absence of effective pharmacotherapy, conventional extracorporeal therapies such as hemodialysis have limited benefit given the ability to remove only water-soluble toxins (3). Given the unique characteristics of the MARS system in removing specific albumin bound serum toxins (including bilirubin) using an albumin dialysate, its application in the treatment of severe cholestatic DILI is mechanistically attractive. A prior case report has shown benefit with early MARS therapy in patients with cholestatic DILI from anabolic steroids (7). With respect to the application of other albumin dialysis therapies, single-pass albumin dialysis and fractionated plasma separation and adsorption systems (Prometheus) may demonstrate similar efficacy to MARS in the treatment of severe cholestatic liver injury (8).

In conclusion, our case series highlights the fact that MARS albumin dialysis could provide an important treatment strategy in the setting of severe refractory cholestatic DILI that currently has limited therapeutic options. Furthermore, knowledge of this dialytic therapy can provide a novel therapeutic option in specific cases of drug and herbal hepatotoxicity in which the causative agent has high protein binding characteristics.

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