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Extracorporeal liver support-albumin dialysis with the Molecular Adsorbent Recirculating System (MARS)

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ABSTRACT

Extracorporeal liver support has been a much studied topic throughout the last 50 years. Albumin dialysis as a therapeutic option for patients with acute liver failure or acute decompensation of chronic liver disease was introduced in the mid-nineties. The Molecular Adsorbent Recirculating System (MARS) is based on the concept of albumin dialysis and allows for the removal of protein-bound as well as water-soluble toxins. Besides its role as a sufficient volume expander human serum albumin is an important scavenger for molecules with pathophysiological relevance in liver failure. Albumin dialysis enables the selective regeneration of patient´s albumin resulting in an increase of albumin binding capacity. Clinically, an improvement of central and local hemodynamics as well as liver-, brain-, and kidney-functions were observed. Thus, the treatment can contribute to liver regeneration and stabilization of vital organ functions and thus help to bridge patients to liver transplantation or to recovery of native liver function. Proper patient selection is critical for clinical success. Aggressive treatment of infections and sepsis seems to be a decisive pre-requisite for its safe and efficient use. Cautious anticoagulation with heparin is the common standard. Citrate use is recommended for patients prone to bleeding. Today, albumin dialysis MARS is among the best studied liver support methods. It appears as a valuable therapeutic tool for the treatment of various complications of of liver failure, especially hemodynamic instability and hepatic encephalopathy. Further studies will need to help defining the optimal patient selection and technical process parameters such as session-length and frequency of treatment.

Key words. Albumin. Liver failure. Hepatic encephalopathy. Hemodynamics.

INTRODUCTION

One hypothesis to explain the pathogenesis of liver failure is that of autointoxication with "liver failure toxins" (Figure 1). Following a primary event damaging the liver (such as acute viral or alcoholic hepatitis, hypoxemia, presence liver toxic compounds) internal and external substances due to be metabolised by the liver accumulate in the blood and tissues of the liver failure patient. Liver support methods are used to remove metabolites that accumulate in the later course of liver failure development due to insufficient clearance by the liver. Early generations of liver support devices were limited in their therapeutic capacity mainly due to lack of efficacy (e.g. in systems using dialysis and hemofiltration) or selectivity (e.g. plasma-exchange and plasma-perfusion over sorbents). Especially the question of membrane structure and pore size in membrane-based methods is of concern. Removal rates for larger target substances increase with increasing pore size. However, selectivity decreases at the same rate what can result in loss of valuable plasma components such as regulator proteins of blood coagulation or growth hormones like hepatocyte growth factor. Ho et al. showed in an elegant plasma filtration study, that survival dramatically decreases in animals with acute liver failure if a regular pore size plasma filter is used as compared to more selective filters.[1] Another relevant aspect of low-selectivity systems is that they are typically not suited for continuous treatment. It was until

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the Mid-nineties that this dilemma between efficacy and selectivity did not allow for real clinical improvement of liver failure patients treated. Introduction of liver cell bioreactors seemed to be an alternative worth studying. However, the observation that the most relevant liver failure toxins are small, hydrophobic molecules depended on transport by human serum albumin, opened a new window of opportunity for the "artificial" liver support systems. In the 1990s several innovative approaches reached the level of clinical studies. The Liver dialysis-method of Ash and colleagues works with a combination of membrane-separation (using a dialysis-membrane) and adsorption.[2] The Prometheus-System (Fractionated Plasma-Separation and –Adsoption, FPSA) follows a similar approach although the separation-membrane was more open (i.e permeable for albumin) and the adsorption was done through fixed columns rather than a moving sorbent suspension.[3] Another technical approach to albumin-cleansing is presented by a method called albumin dialysis. The basis of this technology is formed by the fact, that albumin-bound substances ("liver toxins") can be dialysed through a regular dialysis membrane if the dialysate contains clean albumin as a molecular acceptor. Albumin dialysis is the first membrane-based liver support that allows both: on the one hand maintaining the selectivity of a regular dialysis procedure by using a small pore membrane and, on the other hand, effective removal of even strongly albumin bound toxins. Two clinically usable modes of albumin dialysis are available today: the Molecular Adsorbent Recirculating System (MARS) and Single Pass Albumin Dialysis (SPAD).[4]

MARS has been available for broad clinical use since 1998. It is the best-studied albumin dialysis method at present time. It comprises of a modified hemodialysis with a high flux membrane permitting passage of hydrophobic, albumin-bound target substances and an albumin-enriched dialysate. This albumin-dialysate is on-line regenerated by passage through a second dialyzer and two adsorber columns (charcoal and anion-exchanger)[5] (Figure 2).

CLEARANCE OF WATER-SOLUBLE AND ALBUMIN-BOUND TOXINS (ABT)

The pattern of substances that can be removed from blood by albumin dialysis is much broader than that of hemodialysis, even if the identical type of dialysis membrane is used. Especially a significant removal of various albumin-bound metabolites and drugs that accumulate in liver or kidney failure, enzyme defects such as protoporphyria, or drug overdose belong to this pattern. Substances that are bound to serum albumin and exert damaging effects in higher concentrations are termed albumin-bound toxins (ABT). Rather different groups of biochemicals belong to this group, including steroid acids (e.g. bile acids), open and closed tetrapyrroles (e.g. bilirubin or protoporphyrin), amino acids (especially aromatic amino acids), glycoside derivatives (e.g. indoxylsulfate), phenols (e.g. paracresol), lipids (short- and medium chain fatty acids such as octanoate), and heterocyclic organic compounds (such as furancarboxylic acid). The range of clearance values for ABT was found to be inbetween 10-60 mL/min.[5] Moreover, albumin dialysis allows for removal of water-soluble and thus dialyzable substances such as smaller proteins (e.g. cytokines like interleukin-6 or tumor necrosis factor alpha), ammonia, creatinine or urea.[6-14]

The clinical relevance of ABT-removal was investigated in detail in a number of animal and clinical trials. Plasmatic nitric oxide (NO), bound to albumin as a nitrosothiol, is responsible for the typical hemodynamic changes of liver failure (hyperdynamic hypotension). NO removal by MARS was demonstrated in several clinical investigations.[15-18] Capability to remove inducers of hepatic encephalopathy such as ammonia, tryptophan, endogenous benzodiazepines renders albumin dialysis a valuable tool for this major complication of liver failure. A constant finding is the removal of bilirubin and bile acids. Both fractions, the conjugated and, to a lesser extent, the unconjugated bilirubin are removed.[19] It was found that MARS changes the plasma bile acid composition towards hydrophilic bile acids.[20] Moreover, significant clearance of a number of proinflammatory and anti-inflammatory cytokines was observed.[7,15,17,21-23] However, this did not always result in decrease of blood cytokine levels.[16,24,25] A probably very important effect of albumin dialysis is an increase of the binding capacity of patient´s albumin. In a group of patients with acute decompensation on top of chronic liver failure (AoCLF) the median binding capacity was 63% (compared with healthy controls 98%, $p < 0.001$). MARS treatments resulted in a significant increase.[26,27] The impact of this effect remains to be investigated. However, better drug binding capacity and internal clearance of ABT can be assumed.

INDICATIONS

Circulatory failure and organ malperfusion in liver failure

A key indication for MARS is the improvement of the hemodynamic situation of the patient both, in acute liver failure (ALF) as well as in AoCLF. Systemic vascular resistance index (SVRI) increases during MARS treatments.[5,7,18] In patients with arterial hypotension this results in an increase in mean arterial pressure (MAP).[5,10,18,29] In ALF, Schmidt, *et al.* found significant increase in SVRI and MAP, resulting in significant decrease of cardiac index and heart rate.[30]

The blood perfusion of single organs improved during MARS treatments considerably. A central phenomenon is the decrease of portal pressure in AoCLF[31] and the improvement of renal blood flow.[5] Increased cerebral perfusion pressure was described in AoCLF.[28]

Hepatic encephalopathy and cerebral edema

Hepatic encephalopathy (HE) is a major complication of both, chronic and acute liver failure. Improvement of HE grade and Glasgow Coma Scale during albumin dialysis belong to the first clinical effects reported (for review see 28). A multicenter randomized clinical trial (RCT) studying MARS in 70 AoCLF patients with HE grade III and IV showed significant advantages of MARS versus standard therapy with regard to time to improval as well as grade of improval of HE.[32] This was confirmed by another randomized clinical trial[16] and in several case series.[7,8,10,12,13,29,33]

A drop in intracranial pressure (ICP) during clinical use of MARS was reported by different groups.[5] No randomized clinical trial has investigated this phenomenon so far. However, in a controlled animal study of MARS in ALF using a pig model based on devascularization of the liver. MARS, initiated two hours after clamping, significantly attenuated the ICP increase. The MARS group had a significantly lower brain water content and brain ammonia concentration.[34,35]

Kidney dysfunction/Hepatorenal syndrome

Several groups reported improvement of kidney function during MARS treatments. This included decrease in creatinine and urea, increase in urin output, and resolution of HRS.[5,12,13,29,36] Results were confirmed in a controlled randomized trial in HRS type I patients.[37] The reason for the improved function is currently unknown. However, a significant decrease in plasma renin was found in AoCLF patients with renal failure treated with MARS. This is not an effect of the substance beeing cleared by the system but rather might reflect improved renal blood perfusion. MARS is increasingly considered as a valuable treatment option for HRS.[38-40]

Liver synthetic dysfunction

Albumin dialysis does not add to synthesis. However, liver capacity to synthetize was observed to improve during phases of MARS treatment.[7,12,33,36] However, this was not a uniform finding in all reports. There are no trials reporting further decrease of synthesis parameters.[41] The plasma clearance of indocyaningreen increased significantly after MARS treatment.[29]

Bridging of ALF-patients to liver transplantation

In ALF patients listed for liver transplantation MARS can be applied as a bridging method to stabilize the patient's condition. Not only was the treatment reported to be safe but patient´s condition improved markedly in a substantial number to such an extent that sustained liver regeneration was achieved. Koivusalo, *et al.* report 56 patients with ALF (29 toxic, 22 unknown, 5 other). All fullfilled liver transplantation criteria or had ingested a lethal dose of a known toxic agent (e.g. paracetamol, Amanita phalloides). Mean number of 3 MARS treatments were performed per patient, target treatment duration was 22 h/session. The 1 year survival was 84%. Recovery of native liver function occurred in 30 pats (1y survival: 79%). In the transplanted group 1 y survival was 94%. In the subgroup of toxic ALF the recovery rate was 76% and 23% in the ALF of unknown origin.[42] Camus, *et al.* found similar results in their liver transplantation-candidates. They treated two times/pat. for 8 hours/session and found a transplantation-free survival of 29%.[33] A number of other groups reported safe and successful bridging to liver transplantation or even recovery of native liver function in their patients,[7,8,43-47] among

others in children.[6] However, not all groups saw native liver recovery.[8,48] In 2008 a multicenter randomised controlled trial in France investigated the role of MARS as a tool to bridge patients with ALF to liver transplantation (compare section on Patient survival below).

Quality of life issues in chronic liver disease (pruritus, fatigue)

Patients with unbearable pruritus restant to medical therapy respond well to MARS treatments. Underlying liver diseases were cholestatic forms of liver disease such as PBC or primary sclerosing cholangitis as well as chronic viral hepatitis. Typically, two single treatments lowered pruritus impressively as was documented by Visual Analog Scale. The relief lasted between several weeks up to three months. However, a number of cases did not respond.[8,36,49-51] The phenomenon cannot be explained fully today. However, selective removal of hydrophobic bile acids leading to a longer lasting shift in the bile acid pattern of the patients was suspected to be a potential mechanism.[20,51]

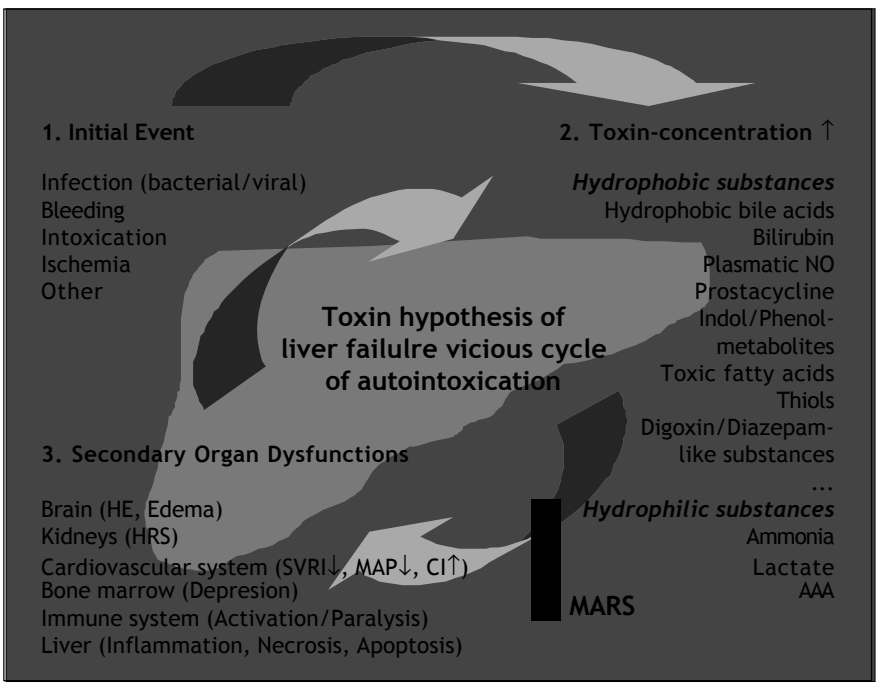

***Figure 1**. The hypothesis of autointoxication in liver failure following a first hit-damage to the liver.*

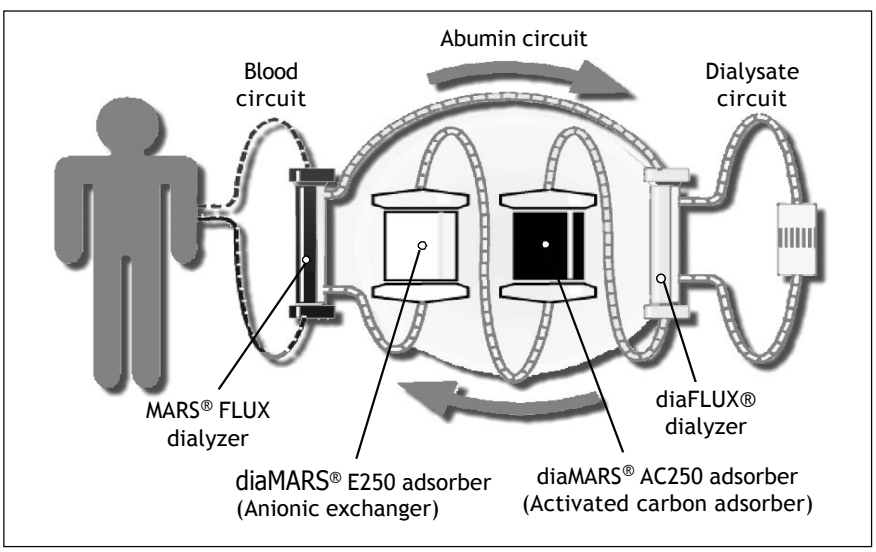

***Figure 2**. The Molecular Adsorbent Recirculating System (MARS) consists of a blood circuit, an albumin circuit, and a dialysate/filtrate side*

Drug overdose/Intoxication

Accidental or suicidal drug overdose resulting in severe, life-threatening intoxications represent an indication for albumin dialysis MARS. The therapeutic goal is either secondary drug removal, if the drug in question is albumin-bound and present in the blood circulation or, what more frequently is the case, to treat drug-induced liver failure. Intoxications and liver failure cases induced by various drugs, e.g. paracetamol or natural toxins, such as amanita toxin, were successfully treated.[42,43,52-54]

PATIENT SURVIVAL

Influence on survival was evaluated in a number of controlled randomized trials so far. In a HRS type I trial including 13 patients significant improvement in survival in the MARS group was reported. Seven day survival was 67% in the MARS *vs.* 0% in the control group. 30 day survival was 25% in the MARS group.[37]

In another randomized trial, MARS was used in patients with postoperative liver failure after heart surgery in a cardiac intensive care setting. In a preliminary report, a clear tendency towards increased survival in the MARS group was observed (7 out of 8 survivers in the MARS group as compared to 1 out of 4 in the control group).[55]

Finally, in 24 AoCLF patients with severe cholestasis (mean bilirubin higher than 30 mg/dL) a significant improvement of 30 day-survival was found (92% in the MARS group *vs.* 50% in the control group, $p < 0.05$).[12]

In clinical cohort trials in AoCLF the MARS group showed significantly better three month as compared to MELD.[13]

A Cochrane Biliary Group analysis of liver support systems from 2003 found a significant 33% reduction in mortality in AoCLF. This effect was mainly carried by the participating MARS studies.[56]

However, the so far largest study performed with MARS in AoCLF patients did not find a difference in survival. The MARS-RELIEF trial, that was first reported at the 2010 meeting of the European Association for the Study of the Liver in Vienna, included patients with acutely decompensated cirrhosis and one or more of the following complications: hepatic encephalopathy, hepatorenal syndrome, and/or progressive hyperbilirubinemia.

Regarding acute liver failure, recently the results of a large multicenter randomised trial of MARS-use in ALF-patients fulfilling high-urgency liver transplant-criteria in France were presented by Saliba and coworkers. Transplant-free 6 month-survival was significantly prolonged in those patients treated with at least three sessions of MARS (AASLD-meeting, San Francisco, Oct 2008). These results confirm smaller studies, that have reported improvement in transplant-free survival in ALF-patients treated with MARS.[33,42]

COST-BENEFIT ANALYSIS

Both, the use of MARS in ALF and in AoCLF was analysed with regard to it's cost utility ratio.

Long-term survival in patients with decompensated liver failure and MARS treatments was studied in the context of health-economic evaluations of the method as well. The first report from 2003 analysed one year-survival in patients with alcoholic liver disease and found a trend towards better survival in the MARS-group.[57] In the three year-follow up of a larger patient group of 149 AoCLF patients a significant survival advantage (33% *vs.* 15%) was found as compared to standard of care with a favourable cost-benefit ratio.[58]

Kantola, *et al.* compared 90 ALF patients treated with MARS from 2001 to 2005 and a historical control group of 17 ALF patients treated from 2000 to 2001. The 3-year outcomes and number of liver transplantations were recorded. Compared to the controls, the average cost per quality adjusted life year safed (QALY) was considerably lower in the MARS group (64,732 euros *vs.* 133,858 euros) within a timeframe of 3.5 years. The authors conclude, that MARS treatment combined with standard medical treatment for ALF in an ICU setting is more cost-effective than standard medical treatment alone.[59]

Last not least, efforts were undertaken to further develop the technology of albumin dialysis to lower treatment costs. In an in vitro-analysis, Drexler et al. determined the optimal dialysate albumin amount to be 100 g rather than 120 g per session, as is the clinical standard today.[60]

TREATMENT RECOMMENDATIONS

Liver support should be considered in AoCLF patients that do not respond to standard of care with several days. In ALF with a high expected mortality rate, commencement of MARS treatment

is recommended as soon as the diagnosis is made. Beyond the indications discussed in detail above, it is important to consider the following points: ALF and AoCLF represent rather different indications for liver support and therefore, different inclusion and exclusion criteria need to be applied. The absence or presence of sepsis and severe disseminated intravascular coagulation seem to devide AoCLF patients in good and bad candidates for MARS. We recommend early and sufficiently aggressive antibiotic treatment of infections as well as antibiotic prophylaxis in those not infected. In AoCLF, very low platelet count (< 50 Gpt/l), high INR (> 2,3), and advanced kidney failure needing dialysis or hemofiltration represent high risk patients that might not take advantage from treatment. In AoCLF, total dosage of treatment should be handeled flexible with days of pausing inbetween, especially if the platelet count is decreasing to values below 50 Gpt/l or INR going above 2,3. The mode should be rather intermittend than continuous with treatment lengths of 6-8 hours per day. In ALF the need for treatment is much bigger and probably continuous treatment with few breaks is most efficient. In ALF much worse INR values can be tolerated than in AoCLF, probably due to the different pathogenesis of INR increase (synthetic defect versus hypercoagulation). Cautious anticoagulation with either small dosages of heparin or with citrate is recommended.[61]

In principle removal of both water-soluble and albumin-bound drugs, e.g. antibiotics need to be considered for the planning of the medical treatment. Basic handling recommendations include dosage application post treatment and therapeutic drug monitoring for blood level surveillance.[5,41]

From todays perspective the correct timing of liver support treatment is of utmost importance for clinical success. Clearly not every patient with AoCLF represents a good candidate for albumin dialysis. We are starting to learn about clinical and laboratory parameter combinations that describe reliable in-and exclusion criteria and serve as indicators for the monitoring and stopping of therapy. However, this process will be an ongoing one for the years to come.

CONCLUSION

There is a clear medical need for better therapies in advanced stages of acute and chronic liver failure. Extracorporeal liver support, through its more than 50 years history of clinical evaluation, has proven to be valuable in treating various complications of liver failure, including hepatic encephalopathy, hemodynamic instability, and progressive hyperbilirubinemia. In many centers it is regular part of liver intensive care therapy. The introduction of albumin dialysis marked a new chapter in the history of liver support systems. Especially the MARS method, that is the most intensely studied artificial liver technology of the last decade, has experienced acceptance and wide clinical use.[41] Data indicate that albumin dialysis allows for safe bridging to liver transplantation and better outcome in primary non-function after transplantation. An encouraging number of ALF-patients recovered native liver function.[33,42] Moreover, there is convincing evidence, that severe decompensation of chronic liver disease represents a good indication for the method.[12,32,37,56]

MARS allows the safe and effective removal of albumin-bound as well as water-soluble substances. Clinically this was accompanied by stable or improved single organ functions and improved overall status of the patient.

CREDITS

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DISCLOSURE OF CONFLICT OF INTERESTS

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