Case Report
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Double Plasma Molecular Adsorption System as Treatment in A Severe Acute-On-Chronic Liver Failure in A Patient with Autoimmune Hepatitis

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ABSTRACT

The use of extracorporeal liver support systems (ECLS) to bridge the patient to liver transplant (LT) or recovery, has been improved in the last years. We present a case of a 55-year female with autoimmune hepatitis who presented liver failure and underwent trough 3 sessions of double plasma molecular adsorption system (DPMAS) as an extracorporeal liver support system. This case illustrates how the use of DPMAS as an ECLD, is safe and effective in reducing bilirubin levels and inflammatory markers in patients with liver failure.
Keywords: *Liver Failure, DPMAS, Extracorporeal Liver Support Systems*

Introduction

Liver failure, acute or acute-on- chronic, is a life-threatening disease with a high mortality rate (Shingina *et al*., 2023). The use of extracorporeal liver support systems (ECLS) would allow support as a bridge to liver transplantation or until the patients' liver can recover or potentially provide symptom relief. ECLS aim to improve detoxification, biosynthesis, regulation, and regeneration, for improving neurological status, hemodynamics, reducing inflammation and enhancing regeneration (van Hoek, 2023). W present case of a patient with acute liver failure who was effectively treated with an extracorporeal liver support, double plasma molecular adsorption system.

Case Presentation

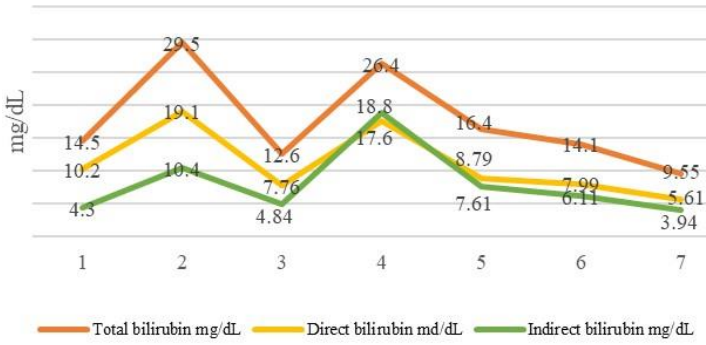
A female 55 years old, diagnosed with autoimmune hepatitis for 4 years, undergoing treatment with hydrocortisone, mycophenolic acid, and ursodeoxycholic acid. With previous exacerbations. Under an incomplete liver transplant protocol. Her current condition began one week prior to admission, presenting with hyporexia, asthenia, and adynamia, accompanied by diffuse colicky abdominal pain with an intensity of 5/10, associated with food intake, without alleviating factors. Physical examination highlights: evident mucocutaneous jaundice, mucocutaneous dehydration, Grade I encephalopathy, and ascites. Cardiorespiratory auscultation was normal. Edema with pitting +++ was noted in the lower extremities. On admission, the following results were obtained from laboratory tests: Hb 8.9 g/dL, Hct 26%, leukocytes 5.30 per µL, platelets 54,000, PT 32.2 s, INR 2.84, aPTT 55.9 s; Cr 0.73 mg/dL; urea 72.8 mg/dL; total bilirubin 14.5 mg/dL, DB 10.2 mg/dL, IB.3 mg/dL; AST 97 U/L; ALT 60 U/L; GGT 43 UI/dL, ALP 135 U/L. With MELD score of 28 points, Child-Pugh class C (13 points). On the fifth day of hospitalization, progression to Grade IV hepatic encephalopathy associated with acute kidney injury KDIGO 2 was observed, with worsening laboratory values: Cr 1.71 mg/dL, BUN 61.7 mg/dL, BT 21.9 mg/dL, BD 15.7 mg/dL.

We performed 3 sessions of DPMAS, on alternate days, with TPE2000 filter cartridge HA330 II and BS 330. Each session lasted for 6 hours and with plasma volume of 1.5 times for DPMAS and 1 time for TPE (Fig. 1) (Connelly-Smith *et al*., 2023). An acute jugular dialysis catheter was used. The associated renal replacement therapy technique was continuous veno-venous hemodiafiltration (CVVHDF). Progressive improvement was observed both in laboratory values and clinical condition after each DPMAS session, which was maintained until the patient's demise, which occurred due to coagulopathy (Table 1 and Graphics 1-2).

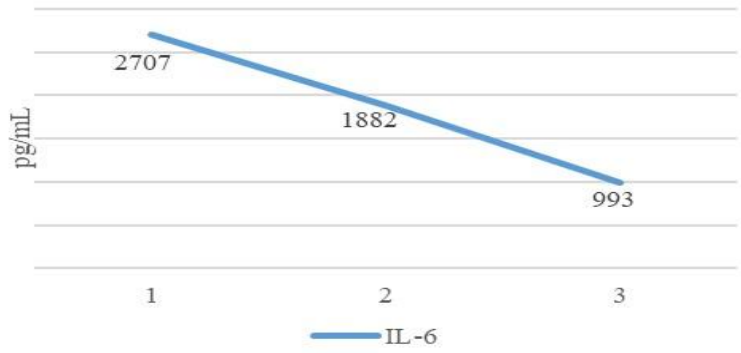
Figure 1: Cartridges BS330 and HA330 II.

Table 1: Laboratory parameters after DPMAS sessions.

Table 1. Laboratory parameters after DPMAS sessions							
Laboratory Parameters	Adm.	**1st session** Qb 130 ml/min Qr post 1400 ml/h		**2nd session** Qb 150 ml/min Qr post 1300 ml/h		**3rd session** Qb 150 ml/min Qr post 1300 ml/h	
		Before	After	Before	After	Before	After
Total bilirubin mg/dL	14.5	29.5	12.6	26.4	16.4	14.1	9.55
Direct bilirubin md/dL	10.2	19.1	7.76	17.6	8.79	7.99	5.61
Indirect bilirubin mg/dL	4.3	10.4	4.84	18.8	7.61	6.11	3.94
AST	97	89	120	97	47	69	42
ALT	60	67	49	45	26	39	31
IL-6	-		2707		1882		993



Graphic 1: Bilirubin levels.



Graphic 2: IL-6 levels.

Discussion

Severe hepatic failure, whether acute or acute- on- chronic, is a life-threatening disease with a high mortality, presenting with encephalopathy, jaundice, coagulopathy and an imbalanced immune system. Even after active treatment, the short-term mortality rate is of 50–90% (Connelly-Smith *et al*., 2023). In liver failure, there are up to 500 different toxins produced, which include, ammonia, urea, bile acids, branched chain aromatic amino acids, reactive nitrate and proinflammatory mediators such as TNF and ILs. Hepatic toxins are often hydrophobic, with a molecular weight <1000 Da. Hyperammonemia is a

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characteristic feature of acute liver failure, ammonia is a small molecule (<0.5 kDa) (Rosa-Diez and Joannes-Boyau, 2023). The management of hyperammonemia does not require adsorption and is performed with high-dose continuous renal replacement therapy (CRRT) (80 mL/kg/h) in association with standard CRRT dose (25–30 mL/kg/h) (Reis *et al*., 2023). The hepatic clearance of bilirubin and bile acids is also impaired in liver failure; but these molecules, despite being small, are covalently bound to blood proteins; like bilirubin (0.406 kDa), cholic acid (0.283 kDa), and chenodeoxycholic acid (0.272 kDa) (Reis *et al*., 2023). This protein binding is a physiological protective mechanism to prevent the free diffusion of bilirubin and bile acids with consequent toxicity in human tissues. These characteristics determine that renal support dialysis techniques based on diffusion and convection are not very useful for its elimination. The elevated bile salts cause renal toxicity and are harmful for bile duct cells and hepatocytes, causing a self-perpetuating mechanism, therefore the removal of these molecules may have a protective role for the liver and kidneys. (Rosa-Diez and Joannes-Boyau, 2023; Reis *et al*., 2023)

In cases of ALF and ACLF, liver transplantation is often required for long- term survival, but there is a scarcity of donor livers and/or disqualification for medical reasons. Within the last years, several therapies have been developed aiming to support liver function to serve as a bridge to transplantation or a replacement therapy while the liver regenerates. The are two main types of devices: artificial and bioartificial (Rosa-Diez and Joannes-Boyau, 2023; Lei *et al*., 2021). The artificial or non- biological is the technique most used in clinical practice. In liver failure, CRRT reduces the risk of ammonia- related neurotoxicity, while ECLS effectively reduce bilirubin and bile acids. The best option to remove albumin-bound toxins, such as bilirubin and bile acids, is a technique that combines plasma filtration with direct adsorption (Rosa-Diez and Joannes-Boyau, 2023; Larsen, 2019; Ostermann *et al*., 2024).

Various systems have been developed, with differences in type of renal replacement therapy, dialysate, membranes, absorption columns, extracorporeal volume and combination with other extracorporeal therapies like high-volume plasma exchange (HVPE) (van Hoek, 2023). Different extracorporeal liver support devices include plasma exchange, SPAD (single-pass albumin dialysis), MARS (molecular adsorbent recirculating system), CPFA continuous plasma filtration adsorption, DPMAS (double plasma adsorption system and Prometheus, a plasma-absorption techniques like fractionated plasma separation and absorption (Rosa-Diez and Joannes-Boyau, 2023). The prognosis of patients following treatment with an artificial liver should be evaluated based on symptoms, laboratory indicators like bilirubin and prothrombin activity, control of complications, end-stage liver disease model score, liver failure grading, and dynamic assessment staging methods (Chen *et al*., 2023). Comparison of ECLSD shows that devices with filtration and direct adsorption relative to albumin dialysis techniques had a significantly

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better removal of protein-bound toxins and water soluble toxins, but similar effects on patient hemodynamics, encephalopathy, and a comparable low incidence of adverse events (Rosa-Diez and Joannes-Boyau, 2023; European Association for the Study of the Liver, 2023).

The DPMAS is a blood purification method that uses adsorbents to bind and non-selectively remove toxins from the blood. This ECLD is based on a technique that combines plasma filtration with direct adsorption; it is the best option to remove albumin- bound toxins. It is proposed to manage acute on-chronic liver failure. The procedure requires the separation of plasma using a hollow fiber plasma filter through a blood pump at 100-200 mL/min. The plasma circuit is moved through the columns by the plasma pump with a velocity of 27–28 mL/min. The plasma will pass through the adsorption column BS330, which the ion exchange resin specific for bilirubin. This is due to electrostatic and lipophilic interactions. After that, the plasma reaches the HA330II hemoadsorption cartridge, a broad-spectrum adsorbent which can adsorb medium- and macromolecular toxins such as inflammatory mediators, such as IL-6 and IL-10. After purification, plasma is reinfused into the body (Rosa-Diez and Joannes-Boyau, 2023; Lei *et al*., 2021; Ostermann *et al*., 2024).

In cases where patients suffer from significantly elevated bilirubin levels or face multiple problems (hyperbilirubinemia, renal insufficiency, water-electrolyte and acid–base disorders), or when plasma sources are inadequate, a combination model is recommended. The combination of DPMAS and PE is one the most commonly combination model. DPMAS can specifically adsorb bilirubin as well as remove inflammatory factors and other toxins without losing autologous plasma, while the combination of PE replenishes coagulation factors and albumin, improves the small amount of depletion of coagulation substances and albumin due to DPMAS, and alleviates the lack of plasma resources. Compared with the application of DPMAS or PE alone, it may increase the removal of toxins such as bilirubin and obtain better therapeutic results (Lei *et al*., 2021; Chen *et al*., 2023).

This therapy has been compared as sole ECLSD and in combination with PE, in patients with acute liver failure, acute-on- chronic failure and cholestatic hepatitis. It has been described that following DPMAS therapy, significant declines were noticed in the total bilirubin, total bile acid and cholesterol; but also the immunomodulatory effect of adsorption (Rosa-Diez and Joannes-Boyau, 2023; Wu *et al*., 2021). The most recent network meta-analysis comparing and ranking different liver support systems and standard medical treatment in patients with ACLF (PROSPERO) included 16 trials and assessed MARS, Prometheus, ELAD, TPE and BioLogic-DT. Overall survival and transplant-free survival were assessed at 1 and 3 months. TPE significantly improved 3-month overall survival compared to SMT (relative risk 0.74; 95% CI 0.6-0.94) and

ranked first on the cumulative ranking curves for overall survival outcomes, at 3 months and 1 month, with 86 an 77% respectively (European Association for the Study of the Liver, 2023).

DPMAS combined with PE therapy can improve liver function, coagulation function, and blood routine level of ACLF patients and increase the effective rate of treatment. Also can effectively reduce the inflammatory response (Rosa-Diez and Joannes-Boyau, 2023; Lei *et al*., 2021). This could be observed in our patient, in whom the bilirubin and IL-6 levels decreased significantly after treatment with DPMAS, from 29.5 mg/dL and 2707 pg/mL, respectively, to 9.55 and 993 pg/mL.

Conclusion

In conclusion, the use of DPMAS as an ECLD, is safe and effective in reducing bilirubin levels and inflammatory markers in patients with liver failure, making it an important option for bridging to liver transplant or liver function recovery.

Statement of Ethics: Written informed consent was obtained at admission from the patient. The study was conducted according to the principles of the Declaration of Helsinki. This manuscript is an honest, accurate, and transparent account of the study, case, or topic being reported; no important aspects have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Consent Form: The patient signed informed consent for the report of this case.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Authors contributions: MZ, RL and LR conceived this study and participated in its design, coordination, wrote the original manuscript. CC, DA and LR revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Data Availability Statement: All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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