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The use of high-flux albumin haemofiltration (HFAF) with Evaclio EC-2C™ in the management of liver failure as a bridge to transplantation

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A 44-year-old male who developed liver failure four years after orthotopic liver transplant was managed using high-flux albumin haemofiltration as a bridge to transplant. The technique, which involves using conventional haemofiltration with a plasma component separator using a filter with a sieving coefficient of 20% for albumin, is described.

Keywords: *liver failure; high-flux albumin haemofiltration*

Introduction

A 44-year-old man developed subacute graft rejection four years after orthotopic liver transplantation. He was suffering profound jaundice, severe pruritis and renal impairment. During an increase in immunosuppressive therapy to control rejection, two treatments using extracorporeal liver support were used.

This treatment is a novel application of high flux albumin filtration (HFAF). Using a selective plasma separation membrane with a 100 kDa cut-off (the Evaclio EC-2C) it is possible to remove the patient's endogenous circulating albumin fraction and bound toxins by haemofiltration and allow replacement with replacement pharmaceutical 4.5% albumin. While this technique may be performed using a conventional continuous renal replacement therapy (CRRT) machine, it is in fact more akin to selective plasma exchange and, unlike conventional CRRT, provides minimal clearance of free water-based substances (eg potassium or urea).

Using HFAF we were able to control jaundice and pruritis and successfully bridge to a second orthotopic liver transplantation. We consider the potential of this technique of extracorporeal support in liver failure and consider the significant clinical advantages and resource implications compared to previously available techniques.

Case report

A 44-year-old man known to the Derby hepatology service was admitted with worsening jaundice, pruritis and renal failure. Four years previously he received an orthotopic liver transplant because of progressive idiopathic small vessel vasculopathy with diffuse ischaemic injury and fibrosis. The graft had functioned well over three years with maintenance immunosupression with mycophenolate, prednisolone and tacrolimus. Over the course of the preceding six months however he had developed non-obstructive jaundice and liver failure. Liver biopsy was suggestive of subacute rejection. His prednisolone and mycophenolate immunosuppressive therapy were increased and tacrolimus titrated to plasma levels and renal function.

During his admission he remained deeply clinically jaundiced with severe, distressing pruritis. This was most marked at night associated with extreme agitation and expressions of suicidal thoughts, and had only partially responded to trials of medical therapy including ursodeoxycholic acid and naloxone infusion. His other blood parameters are detailed in **Table 1**. He was not clinically encephalopathic.

He was referred to intensive care at day 13 post-admission while his immunosuppresive regimen was titrated to control rejection. In an attempt to support his failing liver and alleviate pruritis he was admitted for extracorporeal high flux albumin haemofiltration (HFAF) using the Evaclio EC-2C filter, run on an Infomed HF-440 continuous renal replacement therapy machine. **Figure 1** shows a diagrammatic setup for plasma component exchange using Evaclio. The patient gave informed consent to receiving the procedure and was aware that this was a pilot of a therapy that had not been used in Europe previously.

He received two sessions of six hours' therapy using the prescription shown in **Table 2**. Following each session, complete resolution of pruritis occurred with substantial improvements in jaundice (see **Figure 2**).

After the second course of treatment with HFAF we were unable to offer an intensive care bed and he received Molecular Adsorbents Recirculating System (MARS™, Gambro) therapy under the care of the renal team. After liaison with the regional transplant centre he was transferred, 26 days after hospital admission, and received a second orthotopic liver transplant, which is currently functioning well. His renal function has normalised.

Parameter	Admission 05/01/2010	18/01/2010 16.46 Pre therapy 1	18/01/2010 22.16 Mid therapy 1	19/01/2010 01.17 End therapy 1	19/01/2010 06.14 Off therapy
Bilirubin μmol/L	628	692	480	396	432
Albumin g/L	28	22	25	30	26
Total protein g/L	56	42	41	40	38
Globulin g/L (NR 25-41)	28	20	16	10	12
Total calcium mmol/L	2.39	2.06	2.04	2.14	2.11
ALT	96	58	34	24	24
Gamma GT	120	80	75	70	65
CRP	-	11	-	-	9
Na^+ mmol/L	140	142	-	139	140
K^+ mmol/L	5.2	4.1	-	5.1	4.5
Urea mmol/L	13.0	15.0	-	11.2	12.9
Creatinine mmol/L	127	169	-	138	161
eGFR mL/min	55	39	-	50	42
PT sec (NR 9-13)	19	17*	-	24	18
INR	1.6	1.4*	-	2.0	1.5
Platelets 10^9/L	143	-	-	117	91
Ammonia μmol/L	-	48	-	47	-
Pruritis	Severe	Severe	Severe	Reduced	Absent

Parameter	19/01/2010 23.35 Mid therapy 2	20/01/2010 02.00 End therapy 2	21/01/2010 08.01 30 hours post therapy 2	26/01/2010 07.54 6 days post therapy 2
Bilirubin μmol/L	364	319	435	587
Albumin g/L	29	31	28	22
Total protein g/L	38	39	39	35
Globulin g/L (NR 25-41)	9	8	11	13
Total calcium mmol/L	2.01	2.03	2.06	2.08
ALT	19	14	31	45
Gamma GT	64	60	55	64
CRP	-	-	-	-
Na^+ mmol/L	137	139	140	138
K^+ mmol/L	4.0	4.3	5.0	4.8
Urea mmol/L	15.3	15.1	19.3	18.4
Creatinine mmol/L	194	219	276	253
eGFR mL/min	33	29	22	24
PT sec (NR 9-13)	20	22	-	17
INR	1.7	1.9	-	1.4
Platelets 10^9/L	139	125	99	87
Ammonia μmol/L	-	56	-	-
Pruritis	Moderate	Absent	Severe	Severe

Table 1 Laboratory results before and after high flux albumin haemofiltration with Evaclio EC-2C.
Key: eGFR = estimated glomerular filtration rate, PT = prothombin time, INR = International normalised ratio, CRP = C reactive protein, ALT = alanine aminotransferase, Gamma GT = γ-glutamyl transferase.

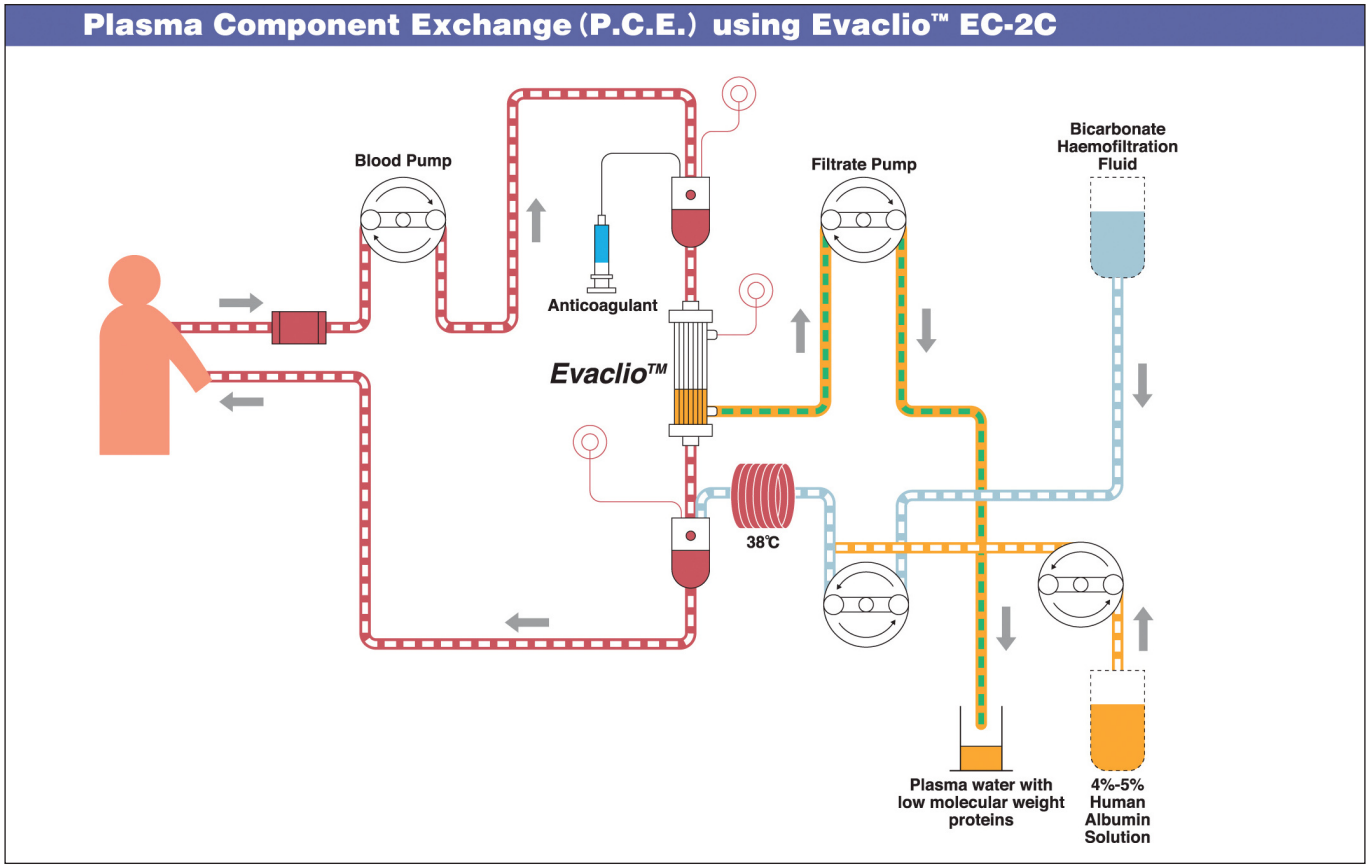

Figure 1 Diagram of the HFAF using Evaclio EC-2C filter.

Parameter	Setting
Blood flow	150-200 mL/minute
Therapy mode	Continuous veno-venous haemofiltration (CVVH) using Infomed HF-440 machine
Filter	Evaclio EC-2C
Therapy details	6 hour treatment, filtration rate 2,500 mL/hr equivalent to a filtrate of 15 L Replacement solution Prismasol-4 2,000 mL/hr and albumin solution 4.5%, 500 mL/hr Automatic adjustment of pre- *vs* post-dilution with transmembrane pressure No fluid removal
Anticoagulation	Localised to circuit 10 IU/kg/hr unfractionated heparin

Table 2 Details of the prescription for the extracorporeal high flux albumin haemofiltration. With a sieving coefficient of 20% for albumin, the volumes were selected to provide an estimated six hour exchange of the patient's endogenous entire albumin volume, ie approximately 3.0 L.

Discussion

Acute and acutely decompensated chronic liver failure (collectively termed ALF) are increasingly common reasons for admission to hospital and intensive care (ICU) and are associated with high mortality.[1] While not implicated in this case, alcohol excess, cirrhosis and subsequent ALF impose a rapidly increasing demand on European ICU resources and such patients often have prolonged ICU admission.[2] The development of multiple organ failure in association with ALF, especially renal failure, has traditionally conferred a poor prognosis, with mortality rates approaching 100%.[3] Many patients with chronic liver failure undergo exacerbations and stabilisation, if not complete recovery, of function, eg following infections. However, if ALF cannot be effectively supported while awaiting recovery, outcomes will be poor, as for most unsupported organ failures. By comparison, 94% of surviving critically ill patients requiring renal replacement therapy recovered renal function at 90 days, including many with chronic renal disease.[4] Patients with ALF and complications, eg hepatorenal syndrome are often managed nihilistically despite rates of recovery in excess of those for sepsis syndromes.[5] The natural history of recovery of liver failure, an organ with impressive powers of regeneration, is largely unknown, as to date a readily available and financially viable mode of liver support has not been available.[6]

Extracorporeal liver support has replicated excretory functions (eg removal of bilirubin and bile acids), although cell culture technologies may provide synthetic capacity and eventually undergo clinical evaluation. It is likely that the costs of such systems will be prohibitive in routine practice for the foreseeable future. Transplantation of auxiliary grafts is an

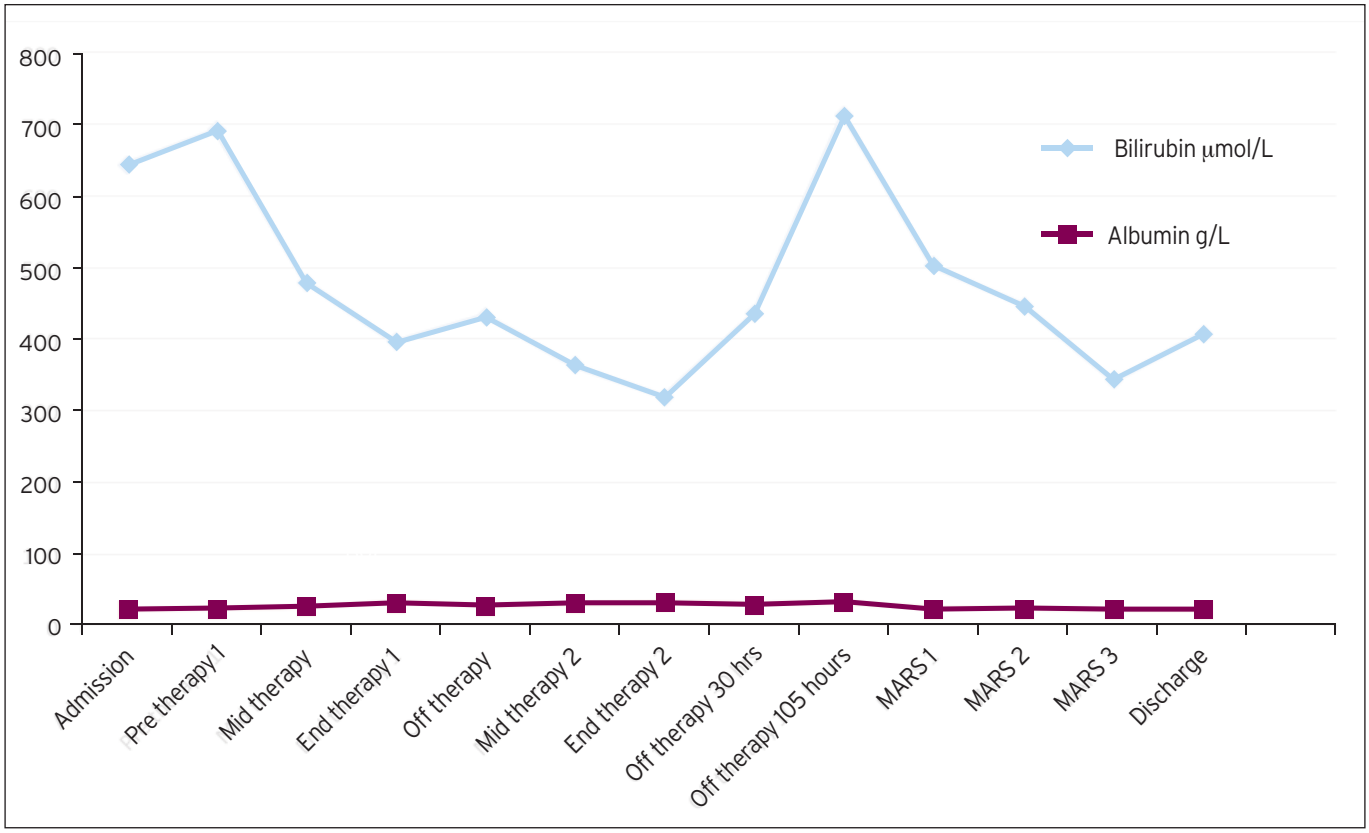

Figure 2 Summary of plasma bilirubin and albumin concentrations during hospital admission.

attractive option but is limited by donor availability and requires immunosupression. Artificial renal elimination by convection and diffusion (haemofiltration and dialysis ie RRT) across synthetic renal membranes is of limited value in liver failure, as most liver toxins are extensively protein-bound and thus not removed by free water elimination, unlike urea, potassium or ammonia. The protein-bound toxins that accumulate in ALF are biochemically diverse; their direct relevance to the pathogenesis of ALF is unclear, but they include porphyrins (eg bilirubin), mercaptans, phenols, bile acids and octanoates. The principal binding proteins for liver toxins are albumin and acid glycoproteins, which are under 100 kDa molecular weight. Animal evidence that accumulation of such toxins impedes hepatic regeneration support the concept that clearance of such liver toxins might promote recovery.[7]

Adaptations to extracorporeal circuits to facilitate toxin removal include charcoal or resin haemoperfusion, albumin-to-albumin dialysis (eg Molecular Adsorption Recirculation System (MARS™) or single pass albumin dialysis (SPAD). MARS has been prominent in European practice but requires expensive specialist equipment and staff with significant running costs,[8] and many regulatory authorities suggest its use only within ongoing studies.[9] Furthermore, toxin clearance may not be assured, requiring transfer to the extracorporeal albumin circuit across a 60 kDa cut-off membrane; ultimately resin and charcoal adsorption columns are the means of elimination. Conventional plasma exchange is effective and requires relatively simple equipment and blood product replacement. However, non-selective filtration of plasma removes liver toxins and binding proteins, but also coagulation factors and immunoglobulins (approximate molecular weight of IgG is 160 kDa, fibrinogen 340,000, IgM 950,000). A more elegant approach is to *selectively* filter plasma and remove the <100 kDa fraction and retain larger proteins within the patient. The Fractionated Plasma Separation, Adsorption and Dialysis system (Prometheus™) presents a 250 kDa cut-off filter coupled with dialysis, but is also expensive and requires specialist equipment. Conversely, the Evaclio EC-2C filter is a plasma component separator produced by Kawasumi Laboratories. It has a sieving coefficient of 20% for presented albumin (ie 20% filtered and 80% retained by the patient) and larger proteins, eg immunoglobulins and coagulation factors, are effectively not filtered.

Therapy based around the Evaclio EC-2C (eg haemodiafiltration) has been described in small series in the Japanese literature[10-14] but this is the first application of HFAF to our knowledge in Europe. The rationale for its use and performance is similar to the Sepet™ system which received United States Food and Drug Administration (FDA) approval for phase 3 evaluation in encephalopathic liver failure, prior to Arbios filing for Chapter 11 bankruptcy protection.[15] The Evaclio EC-2C is a plasma separator membrane but can be driven by a conventional CRRT machine set to continuous haemofiltration (CVVH). Therefore, acquisition costs are significantly lower and training requirements less as the prescription resembles currently used CVVH (**Table 2**). A six-hour session as prescribed will exchange 12.0 L of ultrafiltrate and 3.0 L of albumin, a typical whole plasma volume, which we replaced with 3.0 L of 4.5% pharmaceutical grade albumin.

The system easily allows the option, as with MARS and Prometheus, to perform diafiltration (CVVHDF) to clear water-soluble substances, but since our patient was not significantly uraemic or hyperammonaemic, we omitted dialysis. The comparative costs of filter and replacement fluids will depend upon local pricing arrangements but compare very favourably, including albumin, and are in the region of one-sixth of the cost of a MARS therapy session.

The data presented demonstrate that the removal of the vascular albumin compartment is effective and accompanied by a significant reduction in measured bilirubin. We do not propose bilirubin as a prominent component in the pathogenesis of the syndrome of liver failure, but it is a readily measured marker of albumin-bound toxins and their clearance. The patient also received three days of MARS therapy under the care of the renal physicians, due to bed shortages. While this is not intended as a comparison of MARS and the Evaclio EC-2C, our experience suggests that both therapies significantly reduced bilirubin and alleviated pruritis, and that HFAF is worthy of further investigation.

HFAF proved safe during this limited application. Theoretical changes in albumin and calcium concentrations were not realised, and there was minimal evidence of coagulation activation or systemic inflammation. The stable albumin concentrations confirm previous data for the Evaclio EC-2C albumin sieving coefficient. There was a significant reduction in the plasma globulin fraction, but this was restricted to the alpha and beta fragments, ie the gamma immunoglobulin fraction was maintained. Loss of smaller proteins, eg cortisol or thyroid hormone-binding globulins (molecular weights approximately 50 kDa) will occur and was not assayed. The functional significance of such removal is not known and occurs with other extracorporeal systems, eg MARS, conventional plasma exchange and Prometheus. Our patient had renal impairment prior to HFAF therapy (plasma creatinine 190 µmol/L and estimated glomerular filtration rate (eGFR) 34 mL/minute. Approximately seven days after HFAF therapy, the patient's serum creatinine level peaked at 253 µmol/L with an eGFR of 24 mL/min/1.73m^2. Renal parameters were improved *during* MARS therapy with its dialytic clearance, but approximately 24 hours after MARS, serum creatinine returned to 254 µmol/L and eGFR 24 mL/min. While there are many explanations for this deterioration in renal function, including ongoing liver failure and tacrolimus levels of 26.4 µg/L at the time of initiation of HFAF therapy, the possibility of an impact on renal function will need to be considered in future evaluations.

In summary, HFAF using the Evaclio EC-2C filter was highly effective in controlling liver toxins and symptoms of ALF and was easy to apply and relatively inexpensive. We wish to disseminate its potential applicability in supporting the numbers of critically ill patients with ALF where support with alternative devices, eg MARS is often not offered on the basis of access and cost. A formal prospective evaluation of Evaclio EC-2C therapy is being considered by our Research Ethics Committee, and we would encourage other clinicians with experience of this device to publish their findings. ALF remains perhaps the last major organ failure *without* effective support in critical care, and we propose that HFAF, run via a standard CRRT machine, be evaluated as an effective and conveniently applied therapy in this setting.

Conflict of interests

Linc supported this therapy through supply of free filters, training and running the HF-440 machine during therapy and their medical illustration department provided the extracorporeal circuit diagram. They played no part in patient selection, or preparation of this manuscript.

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