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'Out-patient' albumin dialysis for cholestatic patients with intractable pruritus

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SUMMARY

Background
Intractable pruritus is a major problem for some patients with cholestasis. Albumin dialysis has been shown to ameliorate pruritus, but long-term outcome data are limited.

Aim
To evaluate the safety and efficacy of 'out-patient' albumin dialysis using the molecular adsorbent recirculating system (MARS) in the treatment of intractable pruritus in cholestatic patients referred for liver transplantation for symptomatic relief.

Methods
Fifteen patients who failed to respond to standard medical therapy to control pruritus were included. Three MARS (6 h) sessions were performed per admission, and were repeated, if necessary. The intensity and severity of itch was quantified using itch severity and visual analogue scales (ISS and VAS).

Results
Molecular adsorbent recirculating system treatment was safe and associated with immediate and complete response in 11 patients; two patients had a partial response and two patients had no response. Thirty-four treatments were performed during a follow-up period of 15.7 months (3–46) with patients requiring a mean of two admissions (1–6). The mean VAS and ISS improved significantly (both $P < 0.001$) with improvement in the patient's perception of their quality of life. The duration of acceptable relief in responders was 3.3 months (range 2–5). No serious adverse events were recorded, but the platelet count and haemoglobin were reduced significantly.

Conclusion
Molecular adsorbent recirculating system therapy delivered in an 'out-patient' setting is safe and effective with a high degree of patient acceptability. Albumin dialysis can be considered a viable therapeutic option for patients with severe intractable pruritus, in whom, the only other effective treatment option is liver transplantation.

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INTRODUCTION

Pruritus is a common extrahepatic manifestation of cholestatic liver disease. It is the presenting symptom in 5% of cases of primary biliary cirrhosis (PBC), which is intractable in about 1%.[1] Several mechanisms have been hypothesised to underlie the pathogenesis of pruritus which forms the basis of current approaches to pharmacological interventions. Pruritus is a severely disabling symptom for patients is associated, particularly when present at night, with an overall reduced health related quality of life,[1, 2] considerable psychiatric morbidity,[3–5] and may lead to suicidal ideation in some. Current guidelines for the treatment of pruritus associated with cholestasis, provided by both the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD), recommend cholestyramine as the first line treatment[6] followed by the pregnane X receptor agonist, rifampicin as second line[7] and oral opiate antagonists as third line agents.[8, 9] Both EASL and AASLD recommend all pharmaceutical therapies are attempted in this step-by-step fashion before using any extracorporeal devices, with liver transplantation being a final solution. In PBC patients, the major agent used therapeutically is ursodeoxycholic acid, and this has been proven to delay progression of fibrosis and cirrhosis and diminish the rate of complications of the disease,[10] but there is no evidence showing effectiveness in amelioration of pruritus, and can, in some cases cause worsening of itch.[11] Despite drug therapy, itch is resistant in approximately 5% of patients, in whom liver transplantation is the only available treatment option.[12–15] In most of these patients, liver transplantation is not indicated for severity of liver disease, and is performed for symptom control. The shortage of cadaveric organ donors makes it increasingly difficult to justify transplantation for symptom relief alone. The imbalance between donor supply and need for liver transplantation is likely to grow further, thus requiring an alternative long-term treatment for intractable pruritus.

Albumin dialysis using molecular adsorbent recirculating system (MARS) has been used in many centres to treat intractable pruritus with encouraging results, but as yet, there is limited information on the length of treatment and the duration of amelioration of itch.[13] The main aim of our study was to evaluate the feasibility, safety and efficacy of delivering albumin dialysis as an 'outpatient service' to patients who were referred for liver transplantation for symptom relief. The visual analogue score (VAS) is a simple and validated method for scoring the severity of itch in cholestatic patients. Although it is the current gold standard in assessing and quantifying pruritus, it lacks the qualitative aspects required to determine site, type, intensity of itch and its effects on the overall quality of life. The itch severity score (ISS) has been validated in the Dermatology field, and potentially provides the above qualities.

PATIENTS & METHODS

The patients included in this study provided informed consent, and the study was performed according to the Declaration of Helsinki guidelines.

Patients

Consecutive patients who fulfilled criteria described below are reported in this study. Patients were included in the study if they had chronic cholestatic disease and presented with intractable pruritus, defined as failure to respond to three separate therapeutic agents and were referred for assessment for liver transplantation. They were excluded if they were less than 18 or >80 years, had severe co-morbid diseases, had severe underlying liver disease for which transplantation was thought to be indicated, platelets $<30\ 000 \times 10^9$/L, history of disseminated intravascular coagulopathy, heparin induced thrombocytopenia and lack of consent for treatment.

Patient pathway

Patients follow a map of medicine pathway (Appendix S1) in their referring hospital where drug therapy is optimised. Failure of medical therapy was the reason for referral for liver transplantation. All the patients included in this study had been initially assessed for liver transplantation in various transplant centres, and then referred for albumin dialysis using MARS at our centre. The patients attended the out-patient department where MARS treatment was discussed, previous therapy and their failure recorded and preliminary itch scores are calculated. If they fulfilled criteria, the patient was admitted, central venous dialysis catheter (GamCath, Gambro, Lundia, Sweden) inserted and treatment started. The patient was discharged to the hotel adjacent to the hospital each evening. After 3×6 hourly sessions, the catheter was removed, and patient was discharged home to return when the itch returned to its pretreatment intensity.

Definitions

Response to treatment was defined as a >30% reduction in the itch perception as measured by VAS score which was sustained for longer than 1 month post-treatment.

Partial responders were defined as >30% reduction in itch perception lasting up to 1 month post-treatment. Nonresponders were defined as <30% reduction in itch perception post-treatment. This was used as a means of identifying patients in whom there was no possibility of making a difference to their overall management. We also determined responses in the qualitative domains using the ISS.[18]

Albumin dialysis treatment

We used a standard continuous renal replacement therapy machine, Prisma, (Gambro) which was attached to the MARS monitor (Gambro) in a closed loop albumin circuit. The MARS system has been described elsewhere.[16, 17] It consists of three circuits, a blood circuit, albumin circuit and a renal circuit. Blood is dialysed across an albumin impermeable high flux dialysis membrane (MARS Flux; Gambro Gmbh, Lundia, Sweden). The albumin circuit contains 500 mL of 20% human albumin solution that passes through the dialysate compartment of the MARS Flux membrane. The albumin subsequently passes through a haemodialyser, where it undergoes both haemodialysis and haemofiltration; it is then passed through activated charcoal and anion exchange resin columns to remove acquired toxins.

A venovenous double lumen access catheter (Gambro) was inserted into the internal jugular or femoral vein for blood supply. Intravenous heparin was used as required for blood anticoagulation to prevent clotting in the extracorporeal circuit. The blood flow on the Prisma machine was set to 120–180 mL/min depending on the quality of the access and the haemodynamic profile of the patient. The flow in the closed albumin dialysate circuit was 200 mL/min, and the dialysate and replacement flow was 500 mL/h. Treatment times were 6 h per session for three consecutive days. If clotting of the machine occurred within the first 3 hours, this days session was recommenced. Venous blood samples were taken for measurement of serum bile salts, bilirubin, liver function tests and coagulation.

Assessment of pruritus

Pruritus severity was assessed using two methods:

(i) Standard visual analogue scale: using a 100 mm horizontal line on which the patient is asked to indicate the level of pruritus (0–100, with 0 no pruritus to 100 unbearable itch). This was then verified on a separate scale asking for a simple numerical score between 0 and 10 (0 – no itch, 10 – unbearable).

(ii) Itch severity scale: this scale analyses several components of itch allowing us to see the patients perception of itch.[18, 19] It consists of seven questions relating to frequency, effect on sleep, effect on mood, effect on sexual desire/function, itch intensity using Likert scale[18] and body surface area involvement. The different component responses to each of the seven questions are summed separately and divided by the highest possible total score for the respective question. The seven values are then added together and multiplied by 3 to get a total out of 21. Total ISS scores can range from 0 (no pruritus) to 21 (most severe pruritus) (Appendix S2, ISS scoring system, provided as supporting information).

Pruritus scores were evaluated pretreatment on day 1, immediately post-treatment (session 3), weekly for 4 weeks, and then once per month until repeat treatment was required.

Statistical analysis

Results were expressed as mean ± standard deviation. Significance was tested using paired *t*-test, Wilcoxon's matched-pair test or Mann–Whitney test as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Patients

Fifteen patients were treated with MARS albumin dialysis (predominantly female 13F/2M, PBC: 11, PSC: 3, Other: 1). All 15 patients had intractable pruritus defined as failure to respond to at least three separate therapeutic agents. At the point of treatment, patients were not receiving any additional treatment for their pruritus. The clinical characteristics of the 15 patients are described in Table 1. Thirty-four treatment sessions (102 treatments) were performed on the 15 patients during a median follow-up period of 15.7 (3–46) months with patients requiring a mean of two (1–6) individual admissions for treatment. In the nonresponder or partial responder group, three of the four patients underwent liver transplantation and one is awaiting transplantation. In the responder group ($n = 11$), one patient with advanced liver disease and contraindications for liver transplantation (Patient 2) died and one patient was transplanted (for logistical reasons as the patient's travel to treatment centre was difficult despite MELD score of 6). The other nine responders are undergoing repeated MARS therapy as needed by them for symptomatic relief. One of these patients is now on the waiting list for a transplant

Table 1 | Patient characteristics

Patient	Sex	Age	Aetiology	Bilirubin μmol/L	INR	Albumin g/L	MELD	Failed therapies	Outcome
Patient1	F	45	Secondary biliary cirrhosis	5	0.94	39	6	U, C, O, S, G	Res: MARS
Patient 2	M	75	Post OLT PSC recurrence	150	1.23	26	22	U, C, R, N, P	Res: died
Patient 3	F	45	PBC	28	0.92	43	6	U, C, R, N, S	Res: OLT
Patient 4	F	34	PBC	69	0.94	38	9	U,C,R,N	Res: MARS
Patient 5	F	38	PSC	8	0.94	43	6	C, R,N,O	NR:OLT
Patient 6	F	40	PSC	13	0.97	29	6	C, R,N,O	PR: a/w OLT
Patient 7	F	48	PBC	38	0.98	41	7	U, C, R, N, G	Res: MARS
Patient 8	F	63	PBC	16	1.05	40	6	U, C, R, S, P	Res: MARS
Patient 9	F	51	PBC	63	0.91	40	9	U, C, R, N, P	Res: MARS
Patient 10	F	38	PBC	149	1.85	36	20	U, C, R, N, S, P	*Res: MARS
Patient 11	F	44	PBC	6	0.96	45	6	U, C, R, N, S, G	PR: OLT
Patient 12	M	54	PBC	37	1.05	46	6	U, C, R, N	NR: OLT
Patient 13	F	54	PBC	20	0.91	43	6	U, C, R, S	Res: MARS
Patient 14	F	45	PBC	11	1.05	47	6	U, C, R, N, G	Res: MARS
Patient 15	F	47	PBC	10	0.97	39	6	U, C, R, N, G, P	Res: MARS

MARS, molecular adsorbent recirculating system; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; OLT, orthotopic liver transplant; U, ursodeoxycholic acid; C, cholestyramine; R, rifampicin; N, naltrexone; S, sertraline; G, gabapentin; O, ondansetron; P, piriton; Res, responder; NR, nonresponder; PR, partial responder.

* These patients who responded to MARS are now on waiting list for OLT because of disease progression.

because of progression of their liver disease (Patient 10, bilirubin 149 μmol/L). Overall, the need for transplantation was avoided in eight of the 14 (57%) patients who were potential candidates for liver transplantation with acceptable relief from pruritus.

Safety and tolerance

The overall tolerance of MARS sessions was excellent. There were no serious adverse events, infections, bleeding or hemodynamic changes. Most patients complained of being cold during the first hour of treatment, but this was not sustained. Patient potassium levels decreased, but this was rectified by replacement via the Prisma haemodialysis. Platelet ($P < 0.001$) and haemoglobin ($P < 0.001$) levels dropped significantly in most patients over the three treatment sessions, but did not require treatment. A significant reduction in bilirubin ($P = 0.005$), ALT ($P = 0.017$), creatinine ($P = 0.003$) and ALP ($P < 0.001$) were observed, but no significant difference in INR, albumin or bile salts (Table 2). A haematoma was observed in one patient following line insertion, but her perception was: 'this is a small price to pay for having my life back'.

Table 2 | Changes in biochemical characteristics with MARS (samples taken before first session and after third treatment session)

Parameter	Pre MARS (sem)	Post MARS (sem)	*P* value
INR	1.06 (0.05)	1.065 (0.05)	0.95
Bilirubin μmol/L	76.11 (29.08)	54.35 (18.47)	0.005
Albumin g/L	37.82 (1.74)	37.35 (1.72)	0.541
ALT IU/L	141.42 (56.0)	117.94 (43.67)	0.017
ALP IU/L	431.41 (42.28)	365.53 (32.64)	<0.001
Creatinine μmol/L	86.82 (13.5)	65.17 (5.73)	0.003
Platelets $\times 10^9$/L	246.56 (21.88)	182.82 (15.48)	<0.001
Haemoglobin g/dL	11.65 (0.46)	10.26 (0.4)	<0.001
Bile salts μmol/L	102.83 (29.22)	95.4 (18.59)	0.57

MARS, molecular adsorbent recirculating system.

Efficacy of albumin dialysis on pruritus

Albumin dialysis resulted in relief of pruritus in 13 of 15 patients. All 13 patients who experienced relief showed this immediately post-treatment, the ISS indicated that the severity of itch is reduced in all categories assessed following therapy (Figure 1) with marked improvement in overall quality of life. In two of the 13 patients, the itch had returned to pretreatment values within 1 month and was therefore grouped as partial responders. In the 11 responders, a post MARS ISS reduction of 67% was recorded. Two patients showed less than 30% reduction

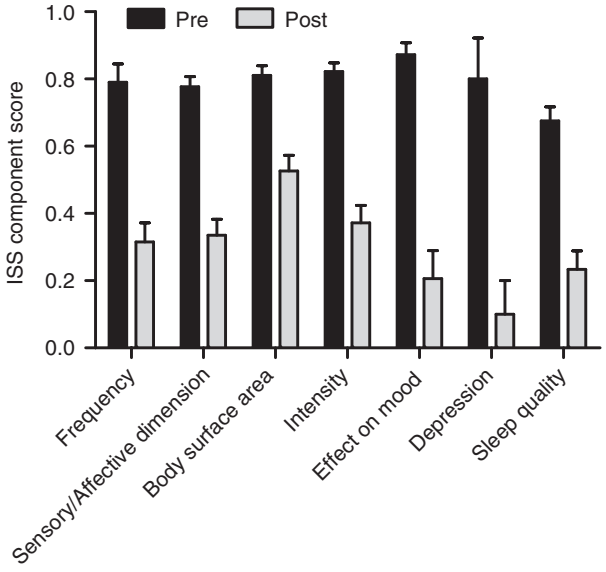

Figure 1 | Changes in the individual components of the itch severity score following treatment with molecular adsorbent recirculating system (MARS) ($P < 0.001$ for each of the fields). Surveys were undertaken before first MARS session and after third treatment session.

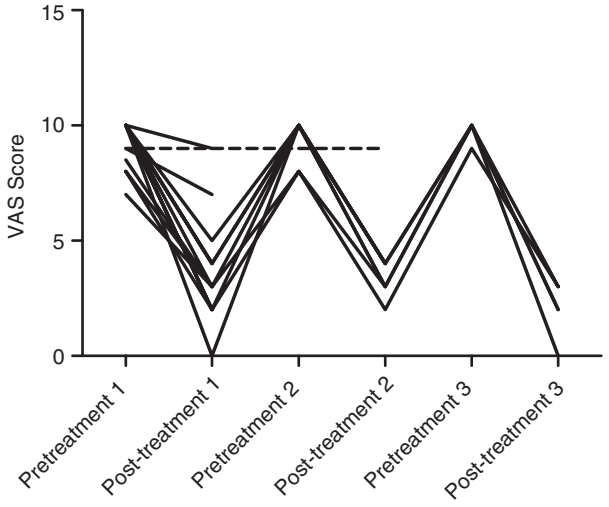

Figure 2 | Changes in the visual analogue score (VAS) for pruritus following treatment with molecular adsorbent recirculating system (MARS). VAS scores were measured before first MARS treatment and after third MARS treatment session. The dotted line shows the nonresponders.

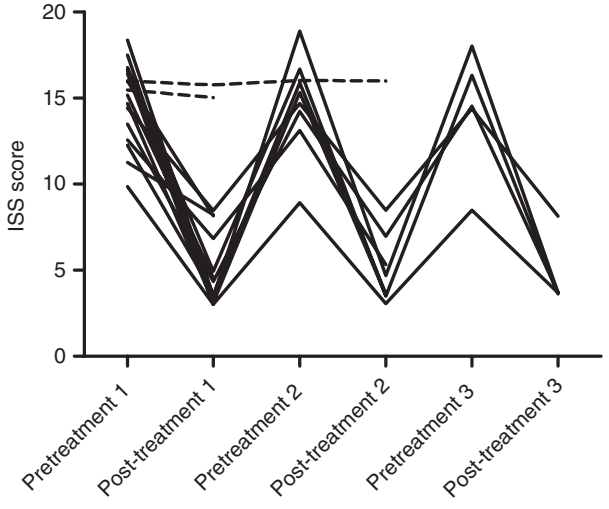

Figure 3 | Changes in the itch severity score (ISS) following treatment with MARS. Surveys were undertaken before first MARS session and after third MARS treatment session. The dotted line represents the nonresponders.

in their ISS post-treatment. The mean VAS pretreatment was 9.4 (0.9) with a mean overall reduction to 4.0 (2.6) post-albumin dialysis. The mean ISS pretreatment was 14.8 (2.5) with mean overall reduction to 6.4 (4.1) post-treatment, results shown in Figures 2 and 3. The VAS/ISS was calculated monthly until the itch had returned to pretreatment levels. The mean duration of acceptable relief in responders was 3.3 months. At 3 month follow-up, the itch had returned in nine of the 13 patients. Pruritus remained tolerable in three patients for up to 6 months. Figures 2 and 3 shows response of individual patients over a period of repeated treatment, demonstrating that when successful in ameliorating itch, this response can be duplicated over a period of time. In one of our patients, this relief has been maintained over 46 months with repeated treatments giving considerable improvement to the patient's perception of their quality of life. When the ISS was broken down to its component parts, there was a significant reduction in all areas, demonstrated in Figure 1, with the greatest reduction being 76.4% effect on mood, patient's perception of depression and anxiety. The smallest change was in the body surface area, and only a 35.1% reduction, the itch is still present in a mild (less intense) form, but patients feel differently about it. Table 3 shows the reduction in itch frequency, sensory and affective dimensions of itch, intensity, depression and sleep quality. The effect of MARS on sexual function was difficult to determine, as this had the highest number of missing data, partly due to being non-applicable in patients out with a relationship and partly due to the inherent reluctance of the patients to

Table 3 | Itch severity scale, individual component reduction

	Pre MARS (0–1)	Post MARS (0–1)	% Reduction	*P* value
Q2 Frequency	0.79	0.31	70.8	0.0007
Q3 Sensory/affective dimension	0.77	0.33	74.6	0.0005
Q4 Body surface area	0.81	0.53	35.1	0.0007
Q5 Intensity	0.82	0.37	54.7	0.0004
Q6 Effect on mood	0.87	0.20	76.4	0.0006
Q7 Depression	0.8	0.1	87.5	0.089 (NS)
Q8 Sleep quality	0.67	0.22	65.4	0.001

MARS, molecular adsorbent recirculating system.

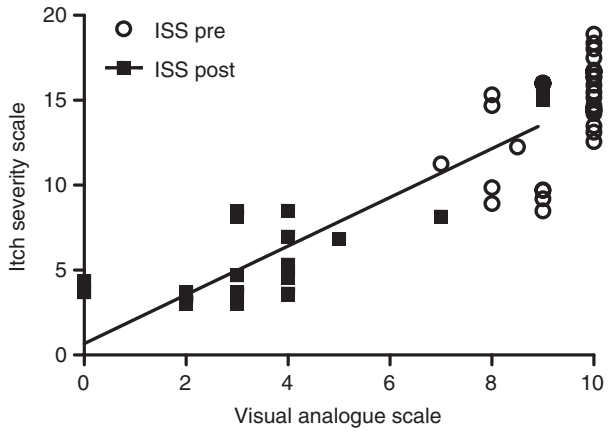

Figure 4 | Shows good correlation between the visual analogue score (VAS) and the itch severity score. (r^2: 0.73; $P < 0.0001$), measured in all patients before first molecular adsorbent recirculating system (MARS) treatment and after third MARS treatment.

disclose details about their sexual function. For those patients who did respond, there was again a significant improvement of 87.5%.

Validation of ISS

There was a strong correlation between the VAS and the ISS in all of the patients ($P = <0.001$, $r^2 = 0.85$) regardless of response. The VAS and ISS reduced proportionately after each treatment session, shown in Figure 4.

DISCUSSION

Molecular adsorbent recirculating system therapy resulted in a significant reduction in the severity of pruritus in patients with severe intractable pruritus and cholestatic liver disease. The patients had failed all available medicinal therapeutic options for controlling pruritus in their referring hospital and all had been referred for transplantation to centres in the UK. Treatment of these patients with MARS was safe (no serious adverse events) and resulted in a significant reduction in pruritus, with a mean reduction of 67% in the responder group for longer than 1 month, two more patients responded partially and had mean of 47% symptom relief for less than 1 month, and two patients had no response to treatment. Failure of adequate response to MARS required liver transplantation in three of the four patients. The need for transplantation could be avoided with repeat therapies in 57% of patients indicating that judicious use of MARS to treat patients with intractable pruritus may allow more organs to be available to transplant sick patients on the waiting list and reduce the morbidity and mortality associated with transplantation.

The pathophysiological mechanisms of pruritus in cholestatic patients are a subject of intense investigation, and therefore, the treatment of pruritus is limited to proposed pathophysiological mechanisms. In cholestatic liver disease, there is no clear relationship between the severity of itching and the severity of liver dysfunction.[20, 21] However, it was not possible to identify on clinical grounds why four of the patients did not respond to MARS or had only very limited response. This may indicate that the mechanisms of pruritus are complex, multifactorial, involving a combination of sensation, perception and reaction, which will make response to a physical intervention such as MARS variable.

Bergasa *et al.* have demonstrated that pruritus of cholestasis is mediated by increased central opioidergic tone, and this has traditionally been the evidence for the use of opiate antagonists.[8] If we consider that dopamine release in the nigrostriatal system is linked to expectation of reward (or the anticipation of therapeutic benefit), we could postulate that all treatments including MARS will result in a release of dopamine and hence an antipruritic effect. However, the sustained benefit seen in 11 of these patients suggests that this is not a placebo effect.

Several investigators have postulated that bile acids are involved in the pathophysiological changes seen in cholestasis, but several lines of investigation indicate that the removal of bile salts alone is unlikely to be associated with amelioration of itch.[21, 22] However, the paper by Pares *et al.*[23] demonstrated a good correlation between the baseline circulating bile acid concentrations and the % change in VAS. As the present study was not designed to examine the bile salts levels, there were no restrictions on food or fasting of patients before baseline samples were taken; they were allowed to eat normally throughout treatment, and this may in part account for the lack of any significant reduction in bile salts. It is unlikely that reduction in bile salts is the sole mechanism by which MARS reduces pruritus as the duration of relief experienced by some patients far exceeds the time for resynthesis of bile salts. The mechanism of improvement of pruritus with MARS therefore remains unclear, but is likely to indicate that severe intractable pruritus is due to accumulation of a possibly protein bound substance that can be removed by albumin dialysis. Indeed, in a preliminary communication, we showed that the improvement in the severity of pruritus with MARS was associated with a reduction in the concentration of autotaxin, which has been suggested as being important in the pathogenesis of pruritus in cholestasis patients.[24] A mean reduction of 27.6% was observed in responders, with no significant reduction in nonresponders. This change in autotoxin activity was directly correlated with the reduction in ISS ($r^2 = 0.59$; $P < 0.005$).[24]

Visual analogue test is a validated test in assessing the severity of the itch, but is subjective and lacks the ability to define the impact of these symptoms on patient's lives. In previous VAS surveys performed, there was a discrepancy in the VAS score which was unchanged in two patients, but verbally, the patients reported significant changes in the severity of pruritus. Furthermore, VAS measurement can potentially be affected by end-aversion/central tendency bias, where there is a tendency to ignore the extreme response options on the scale, because they may be viewed as too strong,[25] and by providing different scales, we expected to reduce if not eliminate this bias. These discrepancies prompted us to use the ISS described by Majeski *et al.*[18] The patients found ISS simple to understand and complete. The VAS and ISS showed a very high level of correlation with a significant reduction in scores in responders and virtually no change in nonresponders. Greater pruritus severity measured using ISS was associated with the patient's perception of poorer quality of life.[18] The affective, but not sensory dimensions of itch were found to be a predictor of depressive symptoms, distress and impairment of sleep,[26] and all of these were measured in the ISS. In 2010, AASLD recommended the use of the newly developed 5D itch scale[29, 30] to assess itch in patients with PBC. 5D scale encompasses the duration, degree, direction, disability and distribution which are very similar to ISS. The author, Elman[30] implied that ISS was not sensitive to change over time; 5-D scale looks at duration of itch in hours per day, the equivalent in ISS is a morning, noon, evening and night tickbox, and this was thought to be adequate and no change in ethical approval was sought to change the scoring system. Following treatment with MARS, the patients experienced improvement of mood (76.4%), improvement of sexual desire (87.5%) and 65.4% described improvement in quality of sleep. Pruritus has been associated with impairment of sleep quality, and psychological symptoms such as depression have been linked to sleep disturbances,[27] making this a very important factor in the patients perception of itch. Lack of sleep in PBC patients is known to contribute to the patient's perception of fatigue.[28] Use of affective descriptors such as unbearable, worrisome and annoying as well as most of the sensory descriptors like stinging, stabbing and burning, were significantly reduced post-treatment. Only about 35% decrease in the body surface area affected by itch was observed in this study, suggesting that surface area is the least important marker for success in treatment as pruritus severity alone did not relate to the patient's perception of their quality of life. If VAS is used to measure pruritus, it remains a subjective symptom, but by ISS, it can better reflect the multi-dimensional character of itching. The assessment of severity as a reflection of subjective factors, in addition to itch intensity provides a more accurate representation of pruritus and the patient's perception of it, thus providing better insight into their quality of life and a more accurate tool for research purposes in assessing therapeutic options. The current scales available for measuring quality of life have not been validated for patients with itch as the primary symptom, but ISS may help fill that gap.

Albumin dialysis is an invasive and expensive procedure with several potential complications including infection and bleeding, the use of which should be restricted to patients who have failed all other pharmaceutical measures. In this era of organ shortages, patients with intractable pruritus, but preserved liver function on the background of cholestatic liver disease should be given a trial of albumin dialysis prior to being considered for liver transplantation. In this group of patients, the need

for transplantation can be avoided in about 57% patients. Albumin dialysis in these cholestatic patients is a symptomatic approach, as the underlying disorders are not reversed by the medical treatment. Although ideally, a double-blind randomised clinical trial should be performed to confirm these observations, sham therapy is ethically difficult to justify. In conclusion, this study shows that a systematic approach for the management of severe intractable pruritus in cholestatic patients using albumin dialysis in specialists centres, delivered in an out-patient setting is a safe, effective and acceptable therapeutic option to both patients and carers that can serve as an alternative to liver transplantation and help improve the supply of valuable organs.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Patient pathway for management of pruritus and MARS therapy.

Appendix S2. Itch severity scale.

Appendix S3. MARS expenditure.

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