Title: Treatment of resistant pruritus from cholestasis with albumin dialysis: Combined analysis of patients from three centers

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Keywords: Primary biliary cirrhosis; Liver-graft rejection; Bile acids.

Abstract

Background & Aims: Albumin dialysis using molecular adsorbent recirculating system (MARS) is a new procedure for treating resistant pruritus from cholestasis, but it is usually published as a case report or a short series. Therefore, we analyzed patients with resistant pruritus treated with MARS from three centers, to assess the changes on pruritus and the indices of cholestasis.
Methods: Twenty patients (12 female, mean age: 51 ± 3.4 years) with chronic cholestatic liver disease or chronic liver-graft rejection were evaluated. The severity of pruritus was assessed using a visual analogue scale (VAS) before and after treatment, and 30 days thereafter. Liver tests, including total bilirubin, alkaline phosphatase, gammaglutamyltransferase, cholesterol, triglycerides, and total bile acid were also determined, as well as the number of sessions and the coupled procedure (dialysis or perfusion). Results: Albumin dialysis resulted in a decrease of pruritus (VAS: from 70.2 ± 4.8 to 20.1 ± 4.2, p <0.001), which partially resumed after 30 days (38.7 ± 6.6). VAS decreased by 72% immediately after treatment and by 51% after 1 month. Pruritus decreased in all but one patient. MARS resulted in a significant bile acid decrease of 41% after treatment and by 37% after 1 month. The effect of MARS on pruritus and markers of cholestasis was similar in patients with different diseases and was independent of the coupled procedure. The improvement of pruritus in individuals was positive in 75% of patients. No major adverse effects were observed.
Conclusions: Albumin dialysis using MARS is an effective procedure for managing resistant pruritus in most patients with chronic cholestasis and graft rejection.

Introduction

Pruritus is a common distressing symptom in patients with cholestasis, particularly in primary biliary cirrhosis (PBC) and in some liver transplanted patients with graft rejection [1,2]. Pruritus can be so severe that it may lead to sleep deprivation and interference with quality of life, and when resistant to the common treatments is an indication for liver transplantation in patients

with chronic cholestatic diseases [3–5].

Current therapeutic options for cholestatic pruritus are directed towards the elimination of presumed peripheral pruritogens by anion exchange resins such as cholestyramine [6] and colestipol or enzyme-inducing agents such as rifampicin [7]. The opioid antagonists, naloxone [8] and naltrexone [9], as well as sertraline [10] have also been shown to alleviate pruritus from cholestasis. In patients who do not respond to medical therapies, different invasive procedures, such as hemodialysis [11], charcoal hemoperfusion [12], and plasmapheresis [13–15] have been used with positive, although uncertain results, due to the small number of patients evaluated. More recently, the therapeutic effects of various methods of extracorporeal albumin dialysis [16–28], mainly the molecular adsorbent recirculating system (MARS), have been published [16–27]. However, from these case reports or short series (the highest has included seven patients) [21], it is difficult to ascertain the actual efficacy of the procedure in patients with cholestatic pruritus. Therefore, the current study analyses the effect of MARS in a series of 20 patients with resistant pruritus from cholestasis, including the overall feeling of satisfaction with the procedure and the changes induced on the indices of cholestasis.

Patients and methods

Patients

We have assessed the effects of MARS on pruritus in 20 patients (12 female, mean age: 51 ± 4.3 years) with chronic cholestatic disease (12 patients) and in liver transplanted patients with chronic graft rejection (eight patients). Partial information from patients three and four from Tenerife and Barcelona, respectively, has already been published [19,20]. All the patients have severe pruritus and they had been previously treated with current non-invasive procedures such as resins, rifampicin, or naltrexone with no response. Tables 1 and 2 show baseline clinical and analytical data on all patients, and in those with chronic cholestatic disease (10 patients with primary biliary cirrhosis, one patient with primary sclerosing cholangitis and one patient with Alagille's syndrome), and with graft rejection (eight patients). Data from eight additional MARS treatments performed in five patients (all with PBC) from Barcelona were also assessed. Therefore, the data collected represents information from 28 treatments carried out in 20 patients. In three of these patients albumin dialysis was repeated 5, 10, and 16 months after the first treatment, in another patient the procedure was carried out 4 and 7 months after the first treatment, and in the remaining patient three further albumin dialysis procedures were performed 7, 29, and 43 months after the first treatment.

Pruritus scoring

The severity of pruritus was assessed immediately before and after the treatment in all patients and 30 days thereafter in patients from Barcelona and Malaga. The scoring was made in these two centers

with a visual analogue scale (VAS) consisting of a 100-mm horizontal line on which the patient drew a line to indicate the severity of itching as previously reported [20]. In the other center the assessment of pruritus was assessed using a semi-quantitative scoring system where a score of 3+ indicated continuous pruritus disturbing sleep patterns, 2+ indicated moderate pruritus present most of the time but tolerable and not interfering with sleep patterns, 1+ indicated mild, intermittent pruritus not affecting the patient's routine or sleep pattern, and 0 indicated no itching [7]. The values obtained in the three patients from this center were recalculated and converted to the VAS in 60, and 90, respectively.

At the end of each treatment patients were questioned about the overall feeling of satisfaction with the therapeutic procedure and scored as follows: (i) satisfactory enough to proceed with new treatments if needed, and (ii) unsatisfactory, meaning that the complexity and discomfort of the invasive procedure was not overcome by the improvement of itching

Laboratory determinations

Immediately before and after each treatment, serum samples were taken for determination of standard hematological and liver function tests including total bilirubin, alanine aminotransferase, alkaline phosphatase, and gammaglutamyltransferase. The circulating levels of cholesterol and triglycerides were determined by standard procedures and total bile acid concentration was also measured by radio immunoassay (ICN Biochemical, GmbH, Eschwenge, Germany) in patients from Barcelona. The same analytical measurements were performed 30 days later in all but one patient.

MARS treatment

The Ethical Committee of each centre approved the treatment protocol. After signing a written informed consent, the patients were treated with the MARS procedure. The number and duration of MARS treatments coupled to standard hemodialysis (HD) or continuous renal replacement therapy (CRRT) machines (Prisma, Hospal, Spain) were also recorded. The duration of any single MARS session performed never lasted more than 9 h using either HD or CRRT. In the Hospital Clinic the patients were submitted to 2-, 7-h MARS sessions, 1 day apart, while in the other two centers, patients were submitted to MARS sessions in consecutive days. The number of sessions and the total duration of MARS treatment for the 20 patients are shown in Table 2. Each single MARS session was performed using a double-lumen catheter in a femoral vein for blood access, and the albumin-enriched dialysate contained 600 ml of 20% human serum albumin. The extracorporeal blood flow and MARS flow were maintained between 150 and 250 ml/min and the albumin dialysate was maintained at body temperature to avoid cooling of the patient. A continuous infusion of heparin was used as an anticoagulant.

Statistical analysis

Data are expressed as mean ± SEM. The unpaired Students t-test was used to compare means between groups, and paired t-tests were used to analyze differences between periods in the same patients. Associations between variables were calculated by Pearson test. The probability level of 5% was regarded as statistically significant.

Results

The clinical and biochemical baseline characteristics of the 20 patients are depicted in Table 1. All the cases had severe pruritus before MARS treatment and biochemical determinations of severe cholestasis with high alkaline phosphatase and gammaglutamyltransferase levels. Total bilirubin was normal (below 1.2 mg/dl) in 11 patients (55%), and total bile acids were elevated in all 13 evaluated cases. Patients with chronic cholestatic diseases and graft rejection were similar with respect to the severity of cholestasis, although albumin concentration and leukocyte count were lower in those with rejection as compared with those with chronic cholestatic disease (Table 1). Gender was also significantly different with higher number of females in the chronic cholestatic disease group. Twelve and eight patients were treated with coupled HD and CRRT, respectively. An average of 2.2 ± 0.7 MARS sessions and an overall 15.7 ± 1.4 h of duration was per- formed in each patient. The severity of cholestasis was not different when comparing patients from the three centers, or when analyzing patients treated in Barcelona and the other two centers.

Albumin dialysis resulted in a significant decrease of pruritus, which increased again after 30 days in nine cases, although pruritus was still significantly lower than before treatment (Table 3) (Fig. 1). Compared with baseline, the VAS decreased by 72% immediately after treatment, and by 51% after 1 month. Similar results were observed when analyzing the 28 treatments performed in the 20 patients (VAS from 69.3 ± 3.7 to 26.4 ± 4.8 after treatment, and to 40.7 ± 5.6 one month thereafter, $p < 0.001$). Pruritus VAS decreased in all but one patient (94.7%) and the overall pruritus improvement was reported satisfactory by 15 patients MARS treatment resulted in a significant decrease of circulat- ing bile acids after treatment (41% of baseline) and after 1 month (37% of baseline) (Fig. 2). A significant decrease of total bilirubin, cholesterol, and gammaglutamyltransferase was also observed. The effects of albumin dialysis on pruritus and bile acid concentration were similar in patients with chronic cholestatic disease or liver-graft rejection (Table 4) and were not related to the coupled to hemodialysis or CRRT (data not shown). No differences on the effect of MARS were observed among the three centers, although it should be pointed out that bile acids were only mea- sured in one center (Barcelona).

Depending on the improvement of pruritus with respect to baseline values (more or less than 50%) the overall number of treatments performed in the 20 patients was divided into two groups: more than 50% improvement in 19 treatments, and less than 50% improvement in nine treatments. There were no significant differences in the severity of pruritus or in the baseline liver function tests between these two groups, except in bile acid concentration and cholesterol levels, which were significantly higher in patients with poorer pruritus improvement (Table 5). Furthermore, there was a significant inverse correlation between the improvement of pruritus expressed as percent of the baseline VAS

and the baseline bile acid ($r = \_0.58$, $p < 0.01$) and cholesterol concentration ($r = \_0.53$, $p < 0.03$) (Fig. 3). These associations were still better when considering only patients with chronic cholestatic disease ($r = \_0.82$, $p < 0.001$, and $r = 0.55$, $p < 0.03$, respectively).

MARS treatment was also associated with changes in platelet count which decreased after the procedure, an event which was observed when examining results of the first treatment performed in the 20 patients and also when analyzing the 28 treatments. However, platelet count resumed the baseline values 1 month thereafter, and this effect did not result in any clinical consequence. No other adverse effects were observed.

Discussion

The most relevant data of this combined analysis, which includes the largest series of patients with resistant pruritus of cholestasis treated with albumin dialysis using MARS, is that the severity of pruritus decreased in all the patients but one, and that the overall performance of the procedure was considered satisfactory enough in 75% of the cases. The decrease in pruritus intensity was observed in most cases with only two MARS sessions, thus totaling an average of 15 h of treatment during two consecutive days or two 7-h sessions one day apart, which was the protocol established in the center which assembled the higher number of patients. Moreover, the favorable effects on relieving itching were observed not only in patients with chronic cholestatic diseases, mainly PBC, but also in liver transplanted patients with graft rejection, severe cholestasis, and itching, which had not responded to conventional procedures such as cholestyramine or colestipol, or to other second and third level treatments for pruritus such as rifampicin or naltrexone.

Beside these positive effects on pruritus, albumin dialysis was associated with a significant decrease in the circulating total bile acid concentration immediately after the last treatment, but also with lower bile acid concentration one month thereafter. Moreover, the intensity of itching relief correlated with total bile acid and cholesterol levels prior to MARS therapy, thus indicating that the positive response to the treatment was indirectly related to the severity of cholestasis according to the circulating total bile acid levels. This observation is particularly relevant in the patients with chronic cholestatic disease. This result restarts the controversy on the contribution of retained bile acids as a consequence of impaired biliary secretion in the pathogenesis of pruritus in this clinical condition [1,29]; although, from our data a direct effect of the retained bile acids cannot be inferred. Thus, the baseline bile acid concentration was not related with the pruritus VAS since there were patients with relatively low bile acid levels and severe pruritus and vice versa. However, there are further recent data supporting a probable association between bile acids and pruritus. Accordingly, it has been reported that cholylsarcosine, a non-metabolisable conjugated bile acid analogue, induced pruritus in two patients with PBC [30]. Likewise, a link between bile acids and pruritus in cholestasis of pregnancy has recently been reported [31]. Despite these data, there is still much controversy over their role in the pathogenesis of pruritus as the direct pruritogen substance. Nevertheless, circulating bile acid concentration might be considered as a surrogate marker of other pruritogen

substances increased in the circulation as the consequence of impaired biliary excretion.

The correlation between serum bile acid concentration and response to MARS treatment in this study raises another interesting issue. Since most patients were treated with only two MARS sessions, it could be speculated that the number of sessions and the duration of treatment was not long enough to result in decreasing the intensity of pruritus and serum bile acid levels. Because of the indirect association between the pretreatment bile acid and cholesterol concentration and the higher improvement of pruritus with MARS, it could be assumed that both the pre- treatment levels of either serum bile acid or cholesterol concentrations might be the markers for defining the duration and the number of MARS treatments needed for patients with resistant pruritus. This is in accordance with the extraordinarily good immediate response to treatment in 94% of the patients, and with a good rate of satisfaction with the procedure, which was reported by 75% of the patients. Actually, two MARS sessions were performed in most patients, thus suggesting that maybe more than two sessions should be needed to achieve better results in patients with very high circulating bile acid cholesterol concentrations. Further studies should be performed to validate this suggestion. Although a placebo effect of this treatment cannot be discarded because no control group was included, the significant and consistent parallel effect on improving itching and decreasing bile acids and cholesterol levels supports the notion that albumin dialysis using MARS is very effective for treating this unbearable complication of chronic cholestatic diseases. On the other hand, it is rather unfeasible to have a placebo group for comparing this therapeutic approach.

The study, which gathers data from 20 patients with resistant pruritus in whom 28 MARS treatments were performed, supplies additional results with respect to the procedure coupled to the MARS device. This is a unique study with a high enough number of patients and treatments to be able to compare the two therapeutic approaches, standard hemodialysis and continuous renal replacement therapy. Half of the treatments were performed with MARS coupled to standard hemodialysis and the other half with MARS coupled to a continuous replacement therapy machine, both used for a period of time of about 8 h to achieve the maximum MARS efficiency. No differences in the positive effects in relieving pruritus and in the capacity of removing substances like bile acids were observed between the two therapeutic approaches, thus indicating that both coupling procedures have a similar efficacy for treating pruritus of cholestasis. Also, this study, with the highest number of patients and treatments reported, indicates that MARS not only has positive effects in pruritus from chronic cholestatic diseases but also in patients with pruritus resulting from liver-graft rejection and severe cholestasis. The mild differences observed between the two conditions in removing bile acids parallel the baseline divergences observed in the two groups.

In summary, MARS therapy is a treatment option in patients with intractable itching from cholestasis with considerably elevated plasma bile acid concentrations. The procedure was effective in most of the patients even with only two sessions. Furthermore, albumin dialysis with MARS was well tolerated, and therefore this procedure should be considered as the last

rescue step in the patients with pruritus who did not experience favorable results with noninvasive treatments. This can help in avoiding liver transplantation in patients with chronic cholestatic diseases experiencing severe and unbearable itching.

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Table 1. Baseline characteristics of patients with pruritus treated with MARS (before the first treatment).

	Overall *n* = 20	Chronic cholestasis *n* = 12	Graft rejection *n* = 8
Age	51.0 ± 3.4	49.9 ± 4.7	51.7 ± 4.3
Female (%)	12 (60%)	10 (83%)	2 (25%)
Pruritus VAS	70.2 ± 4.3	68.3 ± 5.4	73.1 ± 7.2
Bilirubin (mg/dl)	10.4 ± 3.5	7.8 ± 4.4	14.3 ± 5.9
ALT (l/L)	94 ± 12	97 ± 13	89 ± 20
AP (l/L)	1146 ± 210	1194 ± 202	1078 ± 443
gGT (l/L)	528 ± 128	490 ± 110	582 ± 281
Cholesterol (mg/dl)	303 ± 38	332 ± 45	216 ± 48
Triglycerides (mg/dl)	220 ± 60	225 ± 80	205 ± 49
Bile acid (lM)	40.1 ± 6.6	37.9 ± 4.6	46.8 ± 25.8
Albumin (g/L)	36.0 ± 1.1	38.2 ± 1.1	33.0 ± 1.5*
Prothrombin (%)	91.9 ± 4.3	90.0 ± 6.8	94.6 ± 3.9
Hemoglobin (g/L)	11.5 ± 0.4	12.2 ± 0.5	10.6 ± 0.4**
Leukocyte (cell/10^9)	6.5 ± 0.8	8.0 ± 0.9	4.4 ± 1.0*
Platelets (cell/10^9)	209 ± 22	236 ± 24	169 ± 38

* $p < 0.02$.
** $p < 0.03$.

Table 2. Characteristics, type, and duration of MARS treatment in patients with resistant pruritus.

Center	Patient	Disease	Number of MARS sessions per treatment	Total duration of treatment (hours)	Coupled procedure	Further treatments	Months after the first treatment and coupled procedure
Barcelona	1	PBC	2	14	D	Yes	16 (F)
	2	PBC	2	14	D	No	
	3	PBC	2	14	D	Yes	10 (D)
	4	PBC	2	14	D	Yes	7 (D), 29 (F), and 43 (F)
	5	Alagille	2	14	D	No	
	6	Rejection	2	14	D	No	
	7	PBC	2	14	D	No	
	8	Rejection	2	14	D	No	
	9	PBC	2	14	F	Yes	5 (F)
	10	Rejection	2	14	D	No	
	11	PSC	2	14	F	No	
	12	PBC	2	14	F	Yes	4 (F) and 7 (F)
	13	PBC	2	14	F	No	
Málaga	14	Rejection	2	13	F	No	
	15	Rejection	3	11	F	No	
	16	Rejection	2	18	F	No	
	17	Rejection	2	18	F	No	
Tenerife	18	Rejection	5	40	D	No	
	19	PBC	3	24	D	No	
	20	PBC	1	8	D	No	

PBC: primary biliary cirrhosis; PSC: primary scleronsing cholangitis; D: standard hemodialysis; CRRT hemofiltration: F.

Table 3. Effects of MARS on pruritus and laboratory measurements in overall patients.

	Overall $n = 20$		
	Before	After	30 days
Pruritus VAS	70.2 ± 4.8	20.1 ± 4.2*	38.7 ± 6.6*
Bilirubin (mg/dl)	10.4 ± 3.5	6.7 ± 2.1**	1.9 ± 0.4
ALT (l/L)	94 ± 12	82 ± 9	202 ± 104
AP (l/L)	1146 ± 210	982 ± 147	1024 ± 198
gGT (l/L)	528 ± 128	458 ± 115***	459 ± 115
Cholesterol (mg/dl)	270 ± 21	250 ± 17&	289 ± 28
Triglycerides (mg/dl)	220 ± 60	210 ± 36	207 ± 55
Bile acid (lM)	40.1 ± 6.6	24.1 ± 5.6*	18.7 ± 2.2 (7)**
Albumin (g/L)	36.1 ± 1.1	36.6 ± 1.2	39.5 ± 1.8
Prothrombin (%)	91.9 ± 4.3	94.1 ± 2.8	95.7 ± 3.4
Hemoglobin (g/L)	11.5 ± 0.4	11.1 ± 0.3	12.6 ± 0.4
Leukocyte (cell/10^9)	6.5 ± 0.8	6.5 ± 0.7	9.6 ± 2.4
Platelet (cell/10^9)	209 ± 22	186 ± 20	239 ± 18

* $p < 0.001$.
** $p < 0.02$.
*** $p < 0.01$.
& $p < 0.05$.

Table 4. Effects of MARS on pruritus and laboratory measurements in patients a with cholestatic disease or liver-graft rejection.

	Chronic cholestasis $n = 12$			Graft rejection $n = 8$		
	Before	After	30 days	Before	After	30 days
Pruritus VAS	68.3 ± 5.4	21.9 ± 6.4[*]	35.0 ± 8.3[**]	73.1 ± 7.2	17.5 ± 4.9[*]	43.7 ± 11.4[&]
Bilirubin (mg/dl)	7.8 ± 4.3	4.9 ± 2.5	1.4 ± 0.4	14.3 ± 5.9	9.4 ± 3.8	2.6 ± 1.1
ALT (l/L)	97 ± 13	89 ± 11	109 ± 18	87 ± 20	73 ± 16	414 ± 359
AP (l/L)	1193 ± 202	1063 ± 155	1206 ± 217	1077 ± 443	868 ± 291	537 ± 263
gGT (l/L)	491 ± 110	407 ± 89[&]	576 ± 137	582 ± 282	532 ± 262	145 ± 21
Cholesterol (mg/dl)	290 ± 19	268 ± 15[&]	315 ± 29	216 ± 49	202 ± 39	195 ± 49[&]
Triglycerides (mg/dl)	148 ± 28	160 ± 35	152 ± 29	205 ± 49	243 ± 17	168 ± 13
Bile acid (lM)	37.9 ± 4.6	20.4 ± 5.1[**]	18.6 ± 2.6 (7)[***]	46.8 ± 25.8	35.3 ± 17.6	n.d.
Albumin (g/L)	38.2 ± 1.1	37.6 ± 1.6	40.0 ± 2.6	33.0 ± 1.5	35.1 ± 1.6	32.7 ± 2.2
Prothrombin (%)	90.0 ± 6.9	93.7 ± 4.3	100 ± 0	94.5 ± 3.9	94.7 ± 3.2	87.2 ± 10.9
Hemoglobin (g/L)	12.3 ± 0.5	11.6 ± 0.4	13.0 ± 0.4	10.5 ± 0.4	10.4 ± 0.5	11.6 ± 0.4
Leukocyte (cell/10^9)	8.0 ± 0.9	7.9 ± 0.7	8.2 ± 2.1	4.4 ± 1.0	5.7 ± 1.2	13.5 ± 1.2
Platelet (cell/10^9)	236 ± 24	195 ± 25	269 ± 18	169 ± 38	174 ± 36	179 ± 19

[*] $p < 0.001$.
[**] p 60.01.
[***] $p < 0.02$.
[&] $p < 0.05$.

Table 5. Clinical and analytical data, number of albumin dialysis sessions, total duration of treatment, and procedure coupled to MARS depending on the intensity of pruritus improvement after treatment (percent changes with respect to baseline

	P50% *n* = 19	<50% *n* = 9
Baseline pruritus VAS	69.2 ± 4.8	69.6 ± 5.8
MARS sessions (n)	2.2 ± 0.2	2.0 ± 0
Total duration (hr)	15.6 ± 1.5	14.0 ± 0
Coupled procedure		
Dialysis	11 (58%)	4 (44%)
CRRT	8 (42%)	5 (56%)
Bilirubin (mg/dl)	10.7 ± 3.4	2.1 ± 0.6
ALT ((/L)	89 ± 11	104 ± 11
AP (l/L)	1185 ± 221	1029 ± 118
gGT (l/L)	501 ± 134	476 ± 105
Cholesterol (mg/dl)	258 ± 17	340 ± 18*
Triglycerides (mg/dl)	152 ± 24	202 ± 31
Bile acid (l/L)	32.7 ± 7.0	64.1 ± 10.7*
Albumin (g/L)	35.7 ± 1.1	39.9 ± 0.7*
Prothrombine (%)	91.5 ± 4.5	95.9 ± 3.6

* $p < 0.02$.

Fig. 1. Intensity of pruritus assessed by visual analogue score (VAS) before and after treatment with MARS. (chronic cholestatic patients: black line; graft- rejection: grey line).

Fig. 2. Circulating bile acid concentrations in patients with pruritus before and after treatment with MARS.

Fig. 3. Correlation between pruritus changes after MARS treatment and the baseline circulating bile acid concentration. (r = _0.58, p <0.01) (A) and circulating cholesterol concentration. (r = _0.53, p <0.03) (B).

Fig. 3. Correlation between pruritus changes after MARS treatment and the baseline circulating bile acid concentration. (r = —0.58, p <0.01) (A) and circulating cholesterol concentration. (r = —0.53, p <0.03) (B)