Extracorporeal devices for treatment of refractory pruritus in cholestatic liver disease

Roger Williams^{1,2}

Received: 5 April 2017 / Accepted: 17 May 2017 / Published online: 6 June 2017
© Asian Pacific Association for the Study of the Liver 2017

An invitation to write an editorial around the paper entitled “Charcoal hemoperfusion in the treatment of medically refractory pruritus in cholestatic liver disease” was just too much for me to resist. Since the 1970s and our early work on hemoperfusion for temporary liver support in fulminant hepatic failure, I have had a passionate belief in the value of charcoal and other adsorbents for removal of protein-bound toxic substances [1]. Intractable pruritus defines failure of control by the well-tried sequential regime of bile acid sequestrant (cholestyramine or colesevelam), enzyme-inducing agent (rifampicin), opioid antagonist (naltrexone), and selective serotonin inhibitor (sertraline). It affects a relatively small group of patients with primary biliary cholangitis (PBC), 3–5% only. Nevertheless, for these patients, pruritus can be disabling with poor quality of life, sleep deprivation, and even suicidal ideation. The cause of the severe pruritus has long been a puzzle, as there is no correlation with the severity of the underlying disease. Liver structure and function are often well preserved in these patients, making transplantation—which is the last resort in treatment—difficult to justify.

The cited study on charcoal hemoperfusion identified a series of 13 patients (mostly with primary sclerosing cholangitis) from the Mayo Clinic who were treated over the 15 year period 2000–2015 [2]. They received a median of 5 sessions (1–18) of extracorporeal perfusion a week, each lasting 4 h. Nine of the 15 patients had significant

benefit with marked decrease of severe pruritus; the symptom-free period ranged from 80 to 90 days in six subjects who returned for follow-up. In fact, the Mayo Clinic’s interest in this area goes back to the 1980s with a publication in *The Lancet* on plasma perfusion through USP-charcoal-coated glass beads. Use of plasma avoids adverse hematological side-effects seen with hemoperfusion [3]. Eight patients with intractable pruritus, mainly PBC or benign recurrent intrahepatic cholestasis, had two to three plasma perfusions, each lasting for 4 h, on consecutive days. All patients had prompt relief of pruritus. Measurement of bile clearance across the column allowed calculation of bile acid removal, revealing mobilization from the extravascular compartment and reduction in the total bile acid pool. The duration of the clinical response was variable from 24 h to 5 months and could not be correlated with the amount of bile acid removed, the authors even at that time postulating the presence of another unidentified pruritogen in the plasma of these patients.

Of interest in the recent Mayo Clinic paper are the two patients who had no relief of pruritus with charcoal hemoperfusion but did gain relief when switched to the molecular adsorbents recirculation system (MARS). Use of the latter extracorporeal device—based on albumin dialysis and containing charcoal in the adsorbent circuit—in subjects with intractable pruritus has been described in a number of mainly anecdotal reports or small series since the early 2000s. In 2010, the Barcelona Clinic reported results in 20 patients, most receiving 7 h of treatment on two consecutive days. All but one experienced relief from pruritus [4]. Significant decreases in bile acid level in 41% initially and 37% after 1 month were recorded, and intensity of itching correlated with total bile acid level prior to therapy.

✉ Roger Williams
r.williams@researchinliver.org.uk

¹ The Institute of Hepatology London and Foundation for Liver Research, 111 Coldharbour Lane, London SE5 9NT, UK

² Faculty of Life Sciences and Medicine, King’s College London, London, UK

A further series of 15 patients with intractable pruritus treated with MARS published in 2012 similarly showed excellent results [5]. These were patients who had been referred for liver transplant from centers around the country and were treated at the Royal Free Hospital in London on an outpatient basis (6 h of hemoperfusion on three consecutive days). Thirty-four treatments were performed over a period of 15.7 months, and the duration of response ranged from 2 to 5 months. Interestingly, of the 11 patients who had major relief from pruritus, the need for liver transplant was avoided in 8. Bile salt levels were not measured in this series, and relief of pruritus was shown to correlate with a reduction in serum level of a substance known as autotaxin.

Levels of autotaxin (ATX) were also measured in a small series of MARS-treated patients in Amsterdam as part of a major research program into mechanisms underlying pruritus in PBC and other cholestatic conditions [6–8]. Autotaxin is the enzyme that converts lysophosphatidylcholine (LPC, lysoPC) into lysophosphatidic acid (LPA). By measuring free calcium (Ca^{2+}) in neuronal cell lines, these workers identified LPA in pruritic serum as a major Ca^{2+} agonist and potent neuronal activator, also showing that LPA, when injected intradermally into mice, induced scratch responses.

Serum ATX activity has been shown to be markedly increased in serum of PBC patients and, unlike bile acid levels, correlates closely with pruritus intensity. Levels correlate with treatment responses to cholestyramine and rifampicin, and ATX has been shown to decrease in patients with PBC undergoing temporary nasobiliary drainage in association with relief of the itching (see below), and with the levels returning to those preexistent after removal of the nasobiliary endoscopic drain. Interestingly neither ATX activity nor protein could be found in bile of these patients, leading the authors to speculate that an as-yet-undefined factor undergoing enterohepatic circulation may increase ATX expression in serum.

The simplest extracorporeal approach, and one which has also been shown to be effective in reducing the severity of pruritus, is plasmapheresis with replacement of the patient's plasma by fresh frozen plasma. A recently published study from Poland described its use in 17 consecutive patients with refractory pruritus who underwent 129 plasmapheresis procedures during 40 admissions [9]. Pruritus was quantified using a 10-point numerical rating score (NRS), which was shown to be significantly decreased by treatment. This antipruritic effect persisted throughout the 90-day follow-up period. Rebound was most pronounced in patients with cirrhosis from PBC or primary sclerosing cholangitis (PSC), as shown in Fig. 1. Interestingly, NRS at 90 days was significantly lower than before treatment.

Fig. 1 Time course of itch NRS in cirrhotic and noncirrhotic PBC patients following plasmapheresis. Plasmapheresis led to significant decrease in pruritus. This effect was present 30 days after discharge. Significant rebound of itch was detected 90 days after end of plasmapheresis (copyright permission received)

Retention of bile salts and additional pruritic substances in serum and tissues of patients with intrahepatic cholestasis is clearly the result of impaired excretion into bile. Temporary nasobiliary drainage is another approach by which this can be corrected. Among 27 patients treated with this using an endoscopic approach in a multicenter European study with median duration of 7 days, only 1 did not get relief. In a third of the cases, there was immediate and dramatic remission of pruritus within 24 h of institution of the drainage procedure [10]. Biliary drainage diverts bile away from the ileum, where normally 90% of bile salts are reabsorbed and returned to the liver through the enterohepatic circulation. An alternative and much simpler approach is to block the bile acid transporter (IBAT inhibition) located in the terminal ileum. Oral administration of compound GSK2330672 at dosage of 90 mg twice a day for 14 days was shown to be both effective and well tolerated in a very recently published phase 2a double-blind crossover trial of 22 patients with PBC and symptoms of pruritus [11]. Major reduction in three different itch scores was demonstrated and associated with significant reduction in circulating total and conjugated bile acids and enhanced fecal excretion. Interestingly, there was also a significant reduction in the activity of serum ATX, raising the possibility that interruption of ileal reabsorption of an as-yet-unidentified molecule upregulates ATX activity, blocking of which decreases expression or synthesis of ATX.

This class of agent as well as new-generation anti-LPA and anti-ATX agents may find even greater use in the future in treating patients with PBC [12], along with the licencing of obeticholic acid—a semisynthetic bile salt—as a new agent for use in the 25% of PBC cases that do not show improvement in liver with ursodeoxycholic acid (UDCA). Above a certain dose level of obeticholic acid, pruritus can be a troublesome side-effect. Until there is more clinical information on the long-term value of this or other allied clinical agents in development, the evidence that intractable pruritus can be relieved by extracorporeal systems, of which this editorial is a timely reminder, should not be forgotten.

Compliance with ethical standards

Conflict of interest R.W. declares that he has no conflicts of interest.

References

1. Gazzard BG, Weston MJ, Murray-Lyon IM, Flax H, Record CO, Williams R, Portmann B, Langley PG, Dunlop EH, Mellon PJ, Ward MB. Charcoal haemoperfusion in the treatment of fulminant hepatic failure. *Lancet*. 1974;1:1301–7.
2. Kittanamongkolchai W, El-Zoghby ZM, Eileen Hay J, Wiesner RH, Kamath PS, LaRusso NF, Watt KD, Cramer CH, Leung N. Charcoal hemoperfusion in the treatment of medically refractory pruritus in cholestatic liver disease. *Hepatol Int*. 2016. doi:10.1007/s12072-016-9775-9.
3. Lauterburg BH, Taswell HF, Pineda AA, Dickson ER, Burgstaler EA, Carlson GL. Treatment of pruritus of cholestasis by plasma perfusion through USP-charcoal-coated glass beads. *Lancet*. 1980;2:53–5.
4. Parés A, Herrera M, Avilés J, Sanz M, Mas A. Treatment of resistant pruritus from cholestasis with albumin dialysis: combined analysis of patients from three centers. *J Hepatol*. 2010;2010(53):307–12.
5. Leckie P, Tritto G, Mookerjee R, Davies N, Jones D, Jalan R. ‘Out-patient’ albumin dialysis for cholestatic patients with intractable pruritus. *Aliment Pharmacol Ther*. 2012;2012(35):696–704.
6. Kremer AE, van Dijk R, Leckie P, Schaap FG, Kuiper EM, Mettang T, Reiners KS, Raap U, van Buuren HR, van Erpecum KJ, Davies NA, Rust C, Engert A, Jalan R, Oude Elferink RP, Beuers U. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. *Hepatology*. 2012;2012(56):1391–400.
7. Kremer AE, Martens JJ, Kulik W, Ruëff F, Kuiper EM, van Buuren HR, van Erpecum KJ, Kondrackiene J, Prieto J, Rust C, Geenes VL, Williamson C, Moolenaar WH, Beuers U, Oude Elferink RP. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. *Gastroenterology*. 2010;139:1008–18.
8. Oude Elferink RP, Kremer AE, Martens JJ, Beuers UH. The molecular mechanism of cholestatic pruritus. *Dig Dis*. 2011;2011(29):66–71.
9. Krawczyk M, Liebe R, Wasilewicz M, Wunsch E, Raszeja-Wyszomirska J, Milkiewicz P. Plasmapheresis exerts a long-lasting antipruritic effect in severe cholestatic itch. *Liver Int*. 2017;37:743–47. doi:10.1111/liv.13281.
10. Hegade VS, Krawczyk M, Kremer AE, Kuczka J, Gaouar F, Kuiper EM, van Buuren HR, Lammert F, Corpechot C, Jones DE. The safety and efficacy of nasobiliary drainage in the treatment of refractory cholestatic pruritus: a multicentre European study. *Aliment Pharmacol Ther*. 2016;2016(43):294–302.
11. Hegade VS, Kendrick SF, Dobbins RL, Miller SR, Thompson D, Richards D, Storey J, Dukes GE, Corrigan M, Oude Elferink RP, Beuers U, Hirschfield GM, Jones DE. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. *Lancet*. 2017;389:1114–23.
12. Kremer AE, Namer B, Bolier R, Fischer MJ, Oude Elferink RP, Beuers U. Pathogenesis and management of pruritus in PBC and PSC. *Dig Dis*. 2015;2015(33):164–75.