RESEARCH LETTER

Plasmapheresis in the treatment of chronic fatigue in patients with primary biliary cholangitis

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Introduction Chronic fatigue is an untreatable and incapacitating symptom occurring in various autoimmune conditions. It is associated with a dramatic effect on health-related quality of life (HRQoL).[1] Its origin remains unclear; however, an increasing body of evidence indicates that it is centrally mediated with evident autonomic dysfunction. Moreover, it has been recently postulated that resistin and transforming growth factor β (TGF-β) may play a role in the pathogenesis of chronic fatigue.[2] Primary biliary cholangitis (PBC) may manifest itself with chronic fatigue[3] which does not depend on the stage of the disease. Unlike pruritus, fatigue persists after liver transplantation.[4] Plasmapheresis remains a valid option in the treatment of intractable pruritus in PBC when other modalities fail.[5] We analyzed the effect of plasmapheresis on chronic fatigue in a group of 13 patients with PBC and intractable pruritus.

Methods **Patients** Thirteen clinically stable patients with PBC and intractable pruritus not responding to medical therapy were prospectively enrolled in our center (Medical University of Warsaw). There were 12 women (92.3%); 6 patients (46.1%) had cirrhosis, and the median (range) age was 60 (40–69) years. Plasmapheresis was performed as part of medical therapy in these patients. Additionally, in order to investigate the potential role of resistin and TGF-β in fatigue associated with cholestatic disease, these cytokines were analyzed in 103 patients with PBC, including 99 women (96.1%), at a median (range) age of 52 (28–83) years, and then they were correlated with the PBC-40 score for fatigue. The diagnosis of PBC was based on the criteria of the European Association for the Study of the Liver.[6] All patients were treated with ursodeoxycholic acid at a dose of 13 to 15 mg/kg of body weight.

Appropriate informed consent was obtained from each patient included in the study. The study protocol was approved by the ethics committee of the Medical University of Warsaw and conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Procedures Plasmapheresis was performed in 13 patients with intractable pruritus as previously described using COBE Spectra LRS Turbo, version 7.0 (Caridian BCT, Lakewood, Colorado, United States).[5] Three procedures, usually every other day, were performed during one admission (eg, Monday, Wednesday, Friday). Liver biochemistry, measurements of serum resistin and TGF-β using the enzyme-linked immunosorbent assay (Thermo-Fisher Scientific, Waltham, Massachusetts, United States), and HRQoL questionnaires were administered before and 1 month after the procedure.

Questionnaires on health-related quality of life The PBC-40 is a disease-specific HRQoL questionnaire designed for self-completion by patients with PBC.[7] It consists of 40 questions in 5 domains: cognition, itch, fatigue, social-emotional, and other symptoms, marked on a 5-point scale (1 denotes never and 5 denotes always), with higher scores indicating greater impact and poorer HRQoL. The possible range of each domain is: other symptoms, 7 to 35; itch, 3 to 15; fatigue, 11 to 55; cognitive, 6 to 30; social and emotional, 13 to 65 points. The Patient Health Questionnaire-9 (PHQ-9) is a self-administered screening tool for depressive symptoms as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. The PHQ-9 scores range

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TABLE 1 Study parameters at baseline and after plasmapheresis in a group of 13 patients with primary biliary cholangitis

Parameter	Baseline	Follow-up	Difference	*P* value
Biochemical parameters				
Total bilirubin, mg/dl	1.1 (0.5–4.5)	0.7 (0.5–3.3)	0.02 (–0.1 to 0.04)	0.67
ALP, IU/l	196 (105–315)	265 (109–387)	29.5 (–25.5 to 69.5)	0.39
GGT, IU/l	105 (55–198)	115 (76–169)	26 (–3 to 66)	0.24
ALT, IU/l	59 (35–94)	65 (37–92)	–3 (–9 to 24)	0.70
AST, IU/l	75 (41–98)	65 (35–93)	–6.5 (–19 to 20)	0.81
Resistin, ng/ml	10.8 (9.4–13.5)	9.4 (7.4–13.7)	–0.8 (–6.0 to 3.2)	0.48
TGF-ß, ng/ml	2.0 (1.4–2.8)	2.6 (1.1–3.0)	0.2 (–0.6 to 0.9)	0.72
PBC-40 domain				
Other symptoms, points	21 (18–22)	17 (14–21)	–2 (–4 to –1)	0.02
Itch, points	12 (10–14)	8 (7–11)	–4 (–4 to –1)	0.01
Fatigue, points	38 (32–42)	30 (17–34)	–6 (–11 to –4)	0.004
Cognitive, points	18 (14–19)	16 (13–18)	–1 (–3 to 1)	0.31
Social-emotional, points	39 (26–49)	38 (29–45)	–4 (–5 to 3)	0.23
Numeric Rating Scale				
Numeric Rating Scale, points	8 (8.0–8.0)	5 (3.5–7.5)	–3 (–5.5 to –0.5)	0.009
Patient Health Questionnaire-9				
Patient Health Questionnaire-9, points	10 (6–15)	9 (4–13)	0 (–7 to 3)	0.45
Hospital Anxiety Depression Scale				
Depression, points	6 (5–8)	6 (2–7)	–1 (–4 to 0)	0.04
Anxiety, points	7 (6–9)	7 (5–11)	1 (–1 to 3)	0.39

Data are presented as median (interquartile range).

SI conversion factors: to convert ALP, GGT, ALT, and AST to μkat/l, multiply by 0.0167; total bilirubin to μmol/l, by 17.104.

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, asparagine aminotransferase; GGT, γ-glutamyltransferase

from 0 to 27 points. Scores of 10 or greater have sensitivity and specificity of 88% for major depression, and scores of 5, 10, 15, and 20 points correlate with mild, moderate, moderately severe, and severe depression, respectively.[8]

The Hospital Anxiety and Depression Scale (HADS), originally developed by Zigmond and Snaith,[9] is a commonly used self-administered questionnaire to determine the respondent's levels of anxiety and depression. The scale includes 7 items related to anxiety and 7 items related to depressive symptoms, each scored from 0 to 3 points, with higher scores indicating greater symptom severity. The possible range of both domains is 0 to 21 points.

Pruritus was also assessed by the Numerical Rating Scale (NRS), a 10-point self-report scale, where 0 indicates no pruritus at all and 10, intractable pruritus.

Statistical analysis The Shapiro–Wilk normality test and visual inspection of histograms were used to examine the distribution of quantitative variables. Continuous data were presented as medians and interquartile ranges and categorical data as numbers and percentage. Statistical analysis was performed using the Wilcoxon rank sum test and correlation-coefficient assessed with Pearson or Spearman rank correlation tests, as appropriate (Statistica 13.0, TIBCO Software Inc. 2017, Palo Alto, California, United States). *P* values of less than 0.05 were considered significant.

Results and discussion In the plasmapheresis group, there was a significant amelioration of chronic fatigue after the procedure measured by the fatigue score of the PBC-40. Plasmapheresis also reduced pruritus assessed with the use of both PBC-40 and NRS, improved PBC-40 scores for other symptoms, and improved HADS scores for depression (TABLE 1). No correlation was found between fatigue and pruritus after plasma exchange (rho = 0.36; $P = 0.22$). Plasmaphereses had no significant effect either on liver biochemistry or analyzed cytokines (TABLE 1). There was no correlation between chronic fatigue and resistin or TGF-β before and after plasma exchange (Supplementary material, *Figure S1*). Also, no correlation between chronic fatigue as assessed with the PBC-40 and analyzed cytokines was found in 103 controls with PBC ($r = 0.15$ and $P = 0.29$ for resistin; $r = –0.167$ and $P = 0.24$ for TGF-β).

Chronic fatigue has a profound effect on HRQoL and may lead to extended periods of work absence.[10] It remains untreatable and may occur in

various conditions, usually autoimmune diseases, such as rheumatoid arthritis or multiple sclerosis. In the latter, it is considered by patients as the most debilitating symptom affecting everyday life more than spasticity or bladder dysfunction.[11]

Plasmapheresis provides a long-term reduction of pruritus associated with cholestatic liver conditions.[5] Our results show a beneficial effect of plasmapheresis on chronic fatigue in patients with PBC. This effect did not correlate with the observed improvement in pruritus caused by the procedure. This suggests that the decrease of fatigue induced by plasma exchange could be independent from reduced pruritus, which is a novel finding.

Plasmapheresis was implemented in 13 patients with PBC as a treatment of their intractable pruritus. The impact of this procedure on patient well-being was assessed with questionnaires assessing both disease-specific HRQoL (PBC-40) as well as depression (HADS and PHQ-9). In order to gain more insight into pathogenesis of chronic fatigue in cholestasis, we measured serum levels of 2 cytokines, resistin and TGF-β, which showed the strongest link with chronic fatigue of noncholestatic origin in previous studies.[2] In our study, we analyzed these 2 cytokines in patients who underwent plasmapheresis and in a large group of patients with PBC and various degrees of chronic fatigue. No link between the cytokines and chronic fatigue was found in our study patients.

It can be inferred that plasmapheresis, by its mode of action, eliminates the unknown factor or factors responsible for chronic fatigue in PBC. In turn, this may offer a treatment option for patients who are affected by this devastating symptom the most. Notwithstanding, our findings require validation in a larger group of patients with chronic cholestatic liver diseases.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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