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ORIGINAL ARTICLE

Prednisolone plus S-adenosil-L-methionine in severe alcoholic hepatitis

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Abstract
Purpose/background Severe alcoholic hepatitis (AH) is a life-threatening liver disease with a potential of 30–40 % mortality at 1 month. While steroids remain to be a first line therapy, they provide only about 50 % survival benefit. The aim of the study was to evaluate the efficacy of glucocorticoids plus S-adenosylmethionine (SAMe), as compared to glucocorticoids alone, in patients with severe alcoholic hepatitis.
Methods Forty patients with severe AH were randomized in two groups and enrolled in the prospective trial. Group 1 ($n = 20$) patients received prednisolone 40 mg/daily per os, and group 2 ($n = 20$) patients were managed with prednisolone 40 mg/daily per os plus SAMe 800 mg i.v. treatment. Duration was 28 days.
Results The response rate assessed by Lille model was significantly higher in the prednisolone plus SAMe group (19 of 20; 95 %) than in the prednisolone group (13 of 20; 65 %), $p = 0.044$. Two (10 %) patients died, both from the prednisolone group. There were no lethal outcomes in the prednisolone plus SAMe group. The Kaplan–Meier method showed no significant differences between the two groups ($p = 0.151$, log-rank). Hepatorenal syndrome (HRS) occurred in 20 % in the prednisolone group (4 of 20 patients) while no HRS cases were registered in the prednisolone plus SAMe group ($p = 0.035$).
Conclusions Management of severe alcoholic hepatitis with prednisolone plus SAMe was associated with better therapy response ($p = 0.044$) and less frequent HRS occurrence ($p = 0.035$). Mortality was not significantly lower in the prednisolone–SAMe group than in the prednisolone-only group at 28 days (10 vs. 0 %, $p = 0.151$).

Keywords Alcoholic hepatitis · Prednisolone · SAMe · Hepatorenal syndrome

Introduction

Severe alcoholic hepatitis (AH) is a life-threatening disease, characterized by acute onset of fever, jaundice, tender hepatomegaly and liver failure after prolonged heavy alcohol use, and often occurs in the background of cirrhosis, with an average mortality of approximately 40 % [1]. There is no widely accepted, effective treatment for this ailment. Corticosteroids or pentoxifylline are the current pharmacologic treatment options, but they provide only about 50 % survival benefit. Providing more efficacious therapies for patients with AH is one of the most urgent needs in clinical hepatology [2].

Long-term alcohol consumption leads to oxidative stress, disturbance of hepatocyte metabolism, liver inflammation, modifications in the regeneration process and translocation of bacterial products from the gut microbiota into the portal blood stream. Kupffer cells are of particular importance in ethanol-induced liver injury. Chronic ethanol exposure sensitizes Kupffer cells to the activation by lipopolysaccharides (LPS) via toll-like receptor 4 (TLR4). This sensitization enhances the production of various pro-inflammatory mediators, such as tumor necrosis factor (TNFa) and reactive oxygen species (ROS) that contribute to hepatocyte dysfunction, necrosis and apoptosis of hepatocytes, and the generation of extracellular matrix proteins leading to fibrosis/cirrhosis. This

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situation is accompanied by severe mitochondrial depletion of glutathione, the primary antioxidant in cells. Furthermore, hepatocytes are much more sensitive to TNF-α when their antioxidant reserves are low [3]. Combination therapy with an antioxidant and glucocorticoids would have the advantage of both acting on the inflammatory process and reconstituting cellular glutathione reserves [4].

S-adenosyl-L-methionine (SAMe; AdoMet) is an important, metabolically pleiotropic molecule that participates in multiple cellular reactions as the precursor for the synthesis of glutathione and principle methyl donor for a number of reactions [5]. Although the use of SAMe in patients with ALD has been discussed in a number of previous studies there is no data of using SAMe in severe alcoholic hepatitis. Consider exciting results in experimental animal and in vitro studies we decided to conduct this trial in order to investigate possible benefits of SAMe in clinical practice. We conducted a trial to evaluate the efficacy of glucocorticoids plus SAMe, as compared to glucocorticoids alone, in patients with severe alcoholic hepatitis.

Methods

From September 2013 to June 2015 all patients admitted at two Russian hospitals with suspected severe alcoholic hepatitis were evaluated for eligibility. The inclusion criteria were age of 18 years or older, a Maddrey's discriminant function of 32 or more, average alcohol intake of more than 50 g/day during the 3 months before enrollment, and screening-tests results (AUDIT $\geq$ 8 points and CAGE questionnare $\geq$ 3 points).

Key exclusion criteria were cessation of alcohol consumption for more than 2 months before randomization, SAMe, UDCA or pentoxifillin administration prior to hospitalization, the presence of other causes of liver disease, uncontrolled bacterial infection or gastrointestinal hemorrhage in the previous 4 days, cancer, psychiatric disease, drug abuse and serious cardiac, respiratory, or neurologic disease and previous entry into the study within the preceding 6 months..

Study design

We performed a multicenter, open-label, randomized controlled study. After admission, the patients who met the eligibility criteria were randomized into two groups. Randomization was performed with sequentially numbered envelopes to either standard medical therapy with prednisolone (group A, $n = 20$) or prednisolone plus SAMe (group B, $n = 20$). The experimental scheme was approved by the Institutional Review Board and patients or their relatives signed an informed consent form.

The initial examination included the recording of cardiac frequency, blood pressure, temperature, assessment for hepatic encephalopathy, gastrointestinal hemorrhage, ascites, and jaundice. Alcohol consumption was evaluated with the Alcohol Use Disorders Identification Test (AUDIT) and the CAGE questionnaire [6]. Abdomen computer tomography (CT) was performed when applicable. In almost all patients liver biopsy was counterindicated due to disease severity and prominent hypocoagulation and/or low platelet count. Liver biopsy was obtained in two patients, one from the prednisolone group and one from the prednisolone plus SAMe group. In both cases histological findings refer to that of alcoholic hepatitis.

Patients were monitored daily by physical examination and laboratory tests throughout the study. At baseline, day 7, and day 28, clinical variables and laboratory values were collected to assess the Child–Turcotte–Pugh (CTP), Maddrey score (mDF) and Model for End-Stage Liver Disease (MELD) scores as indicators of liver failure and prognosis. At admission, systematic infectious screening consisted of chest X-ray and blood, urine, and ascites cultures. Lille model was applied to assess therapy response on the 7th day of the therapy [7].

Study treatments

Both groups received 40 mg of oral prednisolone per day for 28 days. For the first 7 days, patients in the prednisolone–SAMe group received intravenous infusions of S-adenosil-L-methionine 800 mg daily. After 7th day intravenous regimen was switched to oral SAMe 1200 mg/day for 2 months. Standard supportive care and nutritional support were given to each patient. The use of acetaminophen, pentoxifylline, or anti-TNF-α treatments was prohibited.

Study outcomes

The primary outcome was survival at 28 days. Prognostic factors for 28-day mortality were examined. The secondary outcomes were survival at 6-month changes in laboratory tests (ALT, AST, γGT, ALP and bilirubin), occurrence of hepatitis complications and adverse events.

Statistical analysis

Descriptive statistics were used to summarize the data. Quantitative variables, expressed as mean ± SD, were compared with the use of the Wilcoxon test, Mann–Whitney U-test, or Student's t test, as appropriate. Qualitative variables, expressed as percentages, were compared with the use of a chi-square test or Fisher's exact test. Kaplan–Meier survival curves were plotted for up to 28 days and

compared with the use of a log-rank test. Factors that were significantly predictive of mortality in a univariate analysis ($p < 0.05$) were included in a multivariate Cox logistic-regression. Statistical analyses were performed by SPSS (Statistical Package for the Social Sciences) 17.0 and p values <0.05 were considered as significant. All reported p values are two-sided.

Results

A total of 169 patients with ALD were evaluated for eligibility, and 63 of them had severe alcoholic hepatitis. Forty patients satisfied the inclusion and exclusion criteria and were enrolled in the study: 20 patients received prednisolone (group A) and 20 received prednisolone plus SAMe (group B).

Groups were comparable in key features, except ALP, which was significantly higher in group B (128.26 vs. 254.95; $p = 0.001$). ALP is known to be a marker of cholestasis and its elevation predominantly associated with distal intrahepatic and extrahepatic bile ducts injury. Since the impact of ALP on the course and outcome of AH is not established and this enzyme is not involved in basic prognostic scores for AH we considered this difference to be negligible (Table 1).

Mortality

After randomization of 40 patients, two (10 %) patients died in the first 28 days, all from the prednisolone group. Both patients were non-responders to prednisolone. There were no lethal outcomes in the prednisolone plus SAMe group in the same period of observation. As regards the secondary outcome, five (25 %) patients had died by 6 months in the prednisolone group, all non-responders and two (10 %) in the prednisolone plus SAMe group: one responder and one non-responder, $p = 0.219$ (Fig. 1).

Response to treatment according to the Lille model and evolution of liver function

Combined treatment with prednisolone and SAMe induced a rapid decrease of bilirubin on the seventh day in comparison to prednisolone only. This improvement in hepatic function was sustained to the end of the treatment period. The magnitude of bilirubin improvement (median decrease in bilirubin at 7 days) was clearly higher in group B patients (prednisolone plus SAMe) than in group A (prednisolone only), i.e. −96.34 vs. −65.40 μmol/L, $p = 0.022$.

Thirty two of 40 patients (80 %) achieved therapy response according to the Lille model. The rate of responders was significantly higher in the prednisolone plus SAMe group (19 of 20; 95 %) than in the prednisolone group (13 of 20; 65 %), $p = 0.044$ (Figs. 2, 3).

Adverse events

Hepatorenal syndrome (HRS) occurred in 20 % in the prednisolone group (4 of 20 patients) while no HRS cases were registered in the prednisolone plus SAMe group ($p = 0.035$). The overall rate of infection was 25 % (5 of

Table 1 Baseline characteristics of the patients

Characteristics	Group A ($n = 20$)	Group B ($n = 20$)	p-value
Sex (M/F)	16/4	11/9	0.91
Age (years)	46.85	46.10	0.839
Alcohol intake g/day	88	70.55	0.188
Duration of alcohol intake (years)	16.95	16.25	0.431
AUDIT score	13.75	15.90	0.309
DF	59.69	79.64	0.06
MELD score	23.40	23.25	0.87
WBC ($\times 10^9$/L)	12.88	13.68	0.623
PLT ($\times 10^9$/L)	167.39	157.07	0.361
ALT (U/L)	54.25	46.40	0.888
AST (U/L)	125.55	110.46	0.473
ALP (U/L)	128.26	254.95	0.001
γGT (U/L)	244.75	378.74	0.966
Albumin (g/L)	26.67	25.47	0.650
Bilirubin (μmol/L)	206.06	232.45	0.865
Creatinine (mg/dL)	1.05	1.0	0.865
Glucose (mg/dL)	5.6	5.1	0.457
Protrombin time (s)	21.9	24.5	0.091

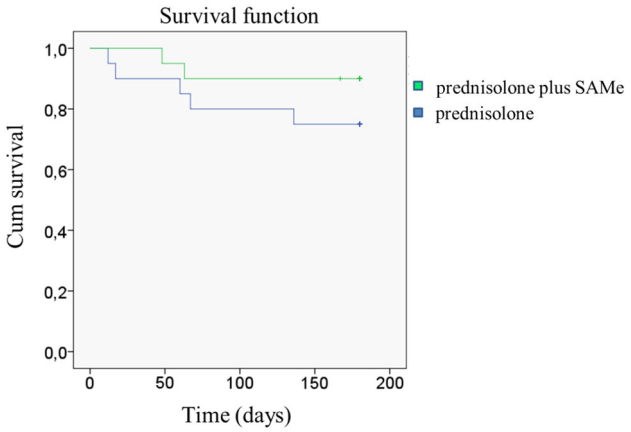

Fig. 1 Kaplan–Meier curves for 180 days survival

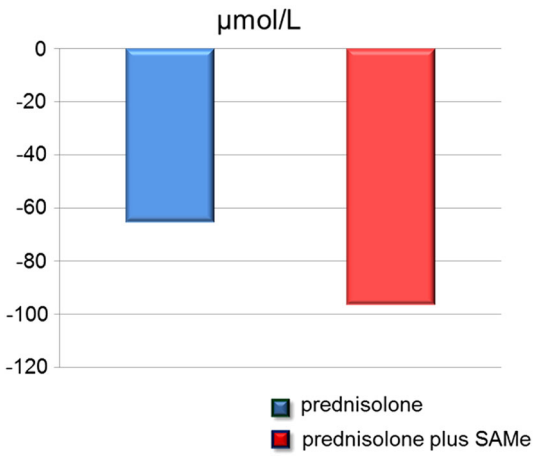

Fig. 2 Median decrease in bilirubin, micromoles per liter

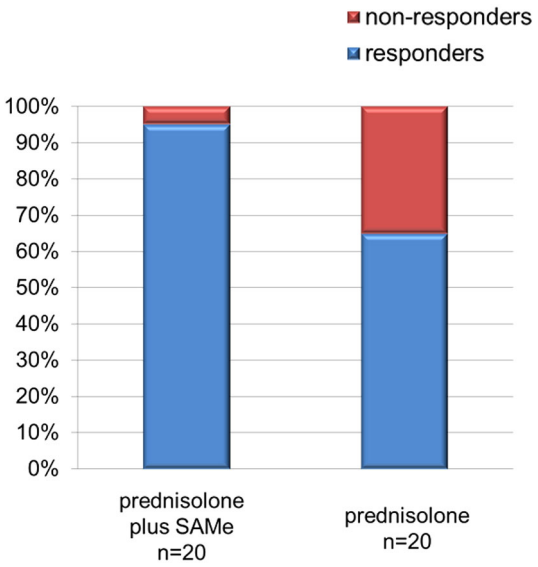

Fig. 3 Therapy response in two groups

20 patients) in the prednisolone group and 30 % (6 of 20 patients) in the prednisolone plus SAMe group ($p = 0.723$). Among patients in the prednisolone group two had nosocomial pneumonia, one had COPD exacerbation and in two patients fungal esophagitis was diagnosed. Patients with bronchial pneumonia and COPD were managed with broad spectrum antibiotics i.v. and patients with fungal infection were given antimycotics. In the prednisolone plus SAMe group four patients had bronchial pneumonia and one had spontaneous bacterial peritonitis, all were treated with antibiotics. Two patients with pneumonia in the prednisolone group died on the 12th and 17th day, respectively. Hyperglycemia occurred in 35 % (7 of 20 patients) in the prednisolone group and was seen in 30 % (6 of 20 patients) in the prednisolone plus SAMe group ($p = 0.185$). The two groups did not differ significantly with respect to other complications.

Discussion

This research was designed to be a pilot study that could explain whether it is safe to use SAMe in severe alcoholic hepatitis and clarify if there are any benefits compared to usual treatment with prednisolone. In this open study, combined therapy with prednisolone plus SAMe markedly improved response to the treatment according to the Lille model (95 vs. 65 %; $p = 0.044$). Although there was no significant difference in short-term survival, therapy with prednisolone plus SAMe showed no lethal outcomes as compared to standard therapy with prednisolone only. Six-month survival was also higher in the prednisolone plus SAMe group (18 of 20 patients, 90 %), compared to the prednisolone therapy alone group (15 of 20 patients, 75 %), $p = 0.219$.

Patients of both groups had high mDF when enrolled in the study with prevalence in the prednisolone plus SAMe group (59.69 vs. 79.64, $p = 0.06$). Even though it is close to significant, we didn't find mDF to predict better prognosis with smaller value if it is higher than the 32-cutoff point. In the largest studies on severe alcoholic hepatitis mDF was used as an inclusion criteria, but not as the tool that can stratify patients if they already have >32 score.

The rationale for the use of antioxidants in the treatment of severe alcoholic hepatitis is based on the principal role of oxidative stress in the disease [8]. Ethanol metabolism leads to accumulation of ROS, which is exacerbated by hypoxia, bacterial translocation and the release of proinflammatory cytokines [9]. Several anti-oxidant enzyme systems scavenge free radicals to mitigate against cellular damage, the most abundant of which is glutathione [10]. Patients with ALD frequently exhibit multiple nutritional deficiencies including protein energy malnutrition and thiamine (vitamin B1),

vitamin B6, vitamin B12, and folate deficiency [11]. These nutrients are essential for normal methionine metabolism and consequently glutathione formation.

As discussed above, SAMe is a precursor for the synthesis of cysteine and thus glutathione. SAMe has been shown to effectively increase intracellular glutathione concentration in murine models [12, 13] and in patients with liver disease [14]. Clinical trials in patients with ALD showed ambiguous results. The largest of these was a 2-year Spanish multi-center study examining the effect of oral SAMe in 123 patients with cirrhosis due to alcoholic liver disease. The survival rate was higher in the SAMe group, 29 vs. 12 % in the placebo group ($p = 0.025$), but only in patients with CTP A and B cirrhosis [15].

The largest study on the use of antioxidants in severe alcoholic hepatitis investigated effect of combined therapy with glucocorticoids plus N-acetylcysteine on survival. This regimen compared to prednisolone significantly improved survival at 1 month (8 vs. 24 %, $p = 0.006$) but not at 3 months (22 vs. 34 %, $p = 0.06$). Death due to the hepatorenal syndrome was less frequent in the prednisolone–N-acetylcysteine group than in the prednisolone-only group at 6 months (9 vs. 22 %, $p = 0.02$) [16].

In the present study combined therapy with prednisolone and SAMe was also associated with significantly less HRS cases, 0 vs. 20 % in the prednisolone group ($p = 0.035$). SAMe could be beneficial in ROS protection in the body because this molecule restores mitochondria levels of glutathione, whereas *N*-acetylcysteine does not [17]. There is evidence that, beyond its effect on hepatocellular ROS, SAMe may have additional beneficial effects modulating the balance between pro- and anti-inflammatory cytokines in liver injury [18].

SAMe combined with corticosteroids appears to be safe and well tolerated in patients with severe alcoholic hepatitis. This combination showed marked lowering of bilirubin level on day 7 compared to usual therapy with prednisolone. Survival rate in the prednisolone plus SAMe group was not significantly higher compared to the prednisolone only group. Nevertheless, better response to the therapy in the SAMe group appears to be a factor of superior survival with significant difference in a larger sample. So, this antioxidant molecule could offer substantial clinical benefits; however, the mechanisms underlying synergistic effect of corticosteroids and SAMe have not yet been fully elucidated. We suppose that after this pilot study larger trials are needed to support or deny SAMe effect on prognosis in patients with severe alcoholic hepatitis.

Compliance with ethical standards

Conflict of interests Petr Evgeniy Tkachenko, Marina Maevskaya, Alexander Pavlov, Inna Komkova, Chavdar Pavlov, and Vladimir Ivashkin declare that they have no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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