Research Article

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Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment

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Background & Aims: Sofosbuvir (SOF) based interferon-alfa free antiviral therapy has become the treatment of choice for patients with chronic hepatitis C virus (HCV) infection. Little is known about safety of drug combinations using two nucleos(t)ide polymerase inhibitors in patients with HCV associated advanced cirrhosis. Here, we report frequent occurrence of lactic acidosis associated with acute-on-chronic hepatic decompensation during ribavirin (RBV) plus SOF based antiviral therapy.

Methods: Thirty-five patients with chronic hepatitis C and advanced fibrosis, compensated cirrhosis, and decompensated cirrhosis without and after liver transplantation were treated with SOF based antiviral therapy with and without RBV. Adverse events including lactic acidosis (pH <7.35, lactate >20 mg/dl) were recorded 24 weeks before and during (mean ± SD, 18 ± 11 weeks) antiviral therapy. Efficacy was determined by assessment of serum HCV RNA.

Results: We observed severe adverse events in 15/35 (43%) patients before (24 weeks) and in 12/35 (34%) patients during antiviral therapy, the majority in association with acute-on-chronic hepatic decompensation. Lactic acidosis occurred in 5/35 (14%) patients during therapy, while no event of lactic acidosis was observed prior to therapy. Lactic acidosis was associated with hepatic decompensation including renal failure and infection, and was severe (pH <7.3) in two patients.

Conclusions: RBV in combination with SOF based antiviral therapy in patients with HCV associated advanced cirrhosis may be associated with the development of lactic acidosis. Impaired renal function, and higher MELD/Child-Pugh scores were identified as potential risk factors.

Introduction

Patients with decompensated liver disease associated with chronic hepatitis C virus (HCV) infection before and after liver transplantation have a poor prognosis, and antiviral therapy is recommended when feasible [1–7]. Sustained virologic response (SVR) rates to (pegylated) interferon-alfa (PegIFNα) based antiviral therapies are lower in those patient cohorts compared to patients with compensated liver disease before liver transplantation [8–10]. Moreover, severity of liver disease and comorbidities may account for contraindications to PegIFNα based antiviral therapy. Therefore, interferon-free therapies are urgently needed in patients with (decompensated) HCV associated cirrhosis and patients prior and after liver transplantation due to HCV. In 2014, interferon-free treatment options became available outside clinical trials for the treatment of chronic HCV and thereby, antiviral therapy can now be offered to a broader spectrum of patients with advanced liver disease and chronic HCV.

Sofosbuvir (SOF) is a potent nucleotide analogue that inhibits the HCV NS5B polymerase with pan-genotypic activity [11–13]. SOF was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in combination with ribavirin (RBV) as the first interferon-free treatment option for patients with chronic HCV with and without contraindications to PegIFNα. Subsequently, three additional direct antiviral agents, simeprevir (SMV), daclatasvir (DCV), and ledipasvir (LDV), have been approved in 2014/2015 for interferon-free treatment regimens in combination with SOF by the FDA and the EMA. Therefore, SOF based antiviral treatment was used in many centers for patients with advanced liver disease before and after liver transplantation.

Keywords: OLT; HCV; Ribavirin; Sofosbuvir; Lactic acidosis.
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Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; APRI, aspartate aminotransferase to platelet ratio index; CP-Score, Child-Pugh-Score, DCV, daclatasvir; EMA, European Medicines Agency; ETR, end of treatment response; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GGT, gammaglutamyltransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; LTX, liver transplantation MELD, model of end stage liver disease; MDRD, Modification of Diet in Renal Disease; (PEG-)IFNα, (pegylated) interferon-alpha; RBV, ribavirin; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TW, therapy week.

Despite the broad use of interferon-free treatment regimens in daily practice in patients with chronic HCV before and after liver transplantation, safety data in these patient cohorts are still limited [14–32]. A number of nucleos(t)ide inhibitors for the treatment of chronic hepatitis B and human immunodeficiency virus (HIV) infection, e.g. abacavir, clevudine, emtricitabine, entecavir, fialuridine, stavudine, or tenofovir, have been associated with mitochondrial toxicity [33–42]. In general, drug-induced mitochondrial toxicity is associated with a wide spectrum of clinical manifestations, including heart failure, myopathy, hepatic insufficiency, pancreatitis, and lactic acidosis. Results of several studies suggest that the likelihood of developing lactic acidosis during nucleos(t)ide analogues therapy in patients with chronic hepatitis B is associated with severity of liver disease, concordant renal insufficiency, and combination therapy with different nucleos(t)ide analogues [33–42]. It is as yet unknown whether SOF based antiviral therapy is associated with lactic acidosis in patients with chronic HCV and advanced liver disease. Here, we report on a series of patients with advanced liver disease who developed lactic acidosis during SOF based antiviral therapy and advanced liver disease before and after liver transplantation.

Patients and methods

Study design

In the current retrospective analysis, 35 consecutive patients with chronic hepatitis C and high priority indication for antiviral therapy, who received a SOF based treatment regimen, were enrolled. To minimize potential bias, all patients with advanced fibrosis, compensated cirrhosis, or decompensated cirrhosis before and after liver transplantation were included, irrespective whether patients were treated within a named patient or a compassionate use program, respectively, or after approval of SOF in Germany. The availability of SOF within the named patients or compassionate use programs was restricted to patients with a high risk of a fatal course and granted only to a small number of patients, who were included in this study (n = 4). The majority of consecutive patients included in the current study was treated after approval of SOF. Therefore, enrolment of patients ranged from October 2012 to July 2014.

Diagnosis of chronic HCV was based on repeated detection of HCV RNA in serum or plasma by a quantitative reverse transcription polymerase chain reaction assay (COBAS TaqMan HCV Test 2.0, Roche Diagnostics GmbH, Mannheim, Germany). Diagnosis of advanced liver fibrosis or cirrhosis was based on histological assessment or liver stiffness evaluated by transient elastography (FibroScan touch 502, Echosens, Bonn, Germany) ⩾12.5 kPa [43,44]. Severity of cirrhosis was assessed by aspartate aminotransferase to platelet ratio index (APRI), Child-Pugh score, model of end-stage liver disease score (MELD score), and evaluation of clinical signs of cirrhosis, e.g. ascites, hepatic encephalopathy, and presence of esophageal varices. Estimated glomerular filtration rate (eGFR) was assessed by Modification of Diet in Renal Disease (MDRD) formula. Adverse events including lactic acidosis were recorded during antiviral therapy at baseline, therapy week (TW) 2, 4, 6, 8, 12, and every 4 weeks if applicable until end of treatment (mean ± SD treatment duration, 18 ± 11 weeks) and intra-individually compared to the respective 24 weeks before initiation of SOF treatment (Fig. 1). Assessment of safety included focused clinical examination and biochemical analyses. Adverse events were classified severe when resulting in hospitalization or prolongation of hospitalization with or without severity classified as life-threatening or cancer development. Lactate and arterial blood pH were measured in all patients with events of acute-on-chronic hepatic decompensation and treatment on the intensive/intermediate care unit. In patients with (severe) adverse events not fulfilling the criteria mentioned above, lactate/pH was obtained only in patients with clinical signs of severe illness at the discretion of the treating physician. Due to the retrospective study design, the interval between lactate level/pH determination and onset of clinical symptoms was not given per study protocol. However, arterial blood lactate levels and pH were measured always timely after admission to the hospital or intermediate/intensive care unit, before effects of therapeutic interventions would have been expected. Lactic acidosis was defined by arterial lactate concentration >20 mg/dl and arterial pH ⩽7.35, and additionally classified severe by a pH <7.30 [45,46]. Antiviral efficacy was assessed by HCV RNA blood analysis at baseline, TW 4, 12, end of treatment, as well as 4 and at least 12 weeks after end of treatment. Informed consent was obtained from all patients enrolled in the present study. Study approval was obtained by the local Ethics Committees for Medical Research in accordance with the 1975 Declaration of Helsinki.

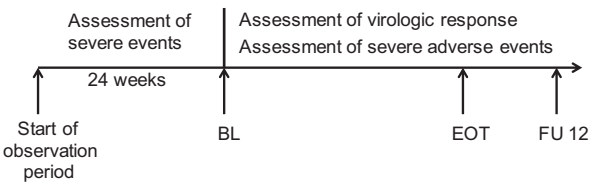

Fig. 1. Study design. Severe adverse events were recorded during antiviral therapy and intra-individually compared to severe events within the immediate 24 weeks before start of treatment. BL, baseline (start of treatment); EOT, end of treatment; FU 12; follow up 12 weeks after end of treatment.

Antiviral treatment schedule

In the current analysis, patients with different SOF based antiviral treatment regimens (SOF + PegIFNα2a + RBV, SOF + RBV, SOF + SMV +/− RBV, SOF + DCV +/− RBV) were included. SOF, DCV, and SMV were administered orally at a daily dose of 400 mg, 60 mg, and 150 mg, respectively. In patients with lactic acidosis or in patients with eGFR assessed by the MDRD formula below 30 ml/min/1.73 m^2 during therapy, SOF was stopped, and restarted, when lactic acidosis or renal function improved within 5 days. No dose reduction was allowed for SOF, and no dose reduction or discontinuation was allowed for DCV or SMV. Four patients were treated within a SOF compassionate use program, and 7 patients were treated within a DCV compassionate use program (study numbers GS-US-334-0152, AI444-237, AI444-EAP). Data of those patients may in part be or will be published within reports of the respective programs. Of note, no data from patients treated within the SOF compassionate use program were reported since the approval of SOF by the EMA.

RBV was given orally according to body weight, renal function, and hemoglobin level. PegIFNα2a was administered at a weekly dose of 180 μg subcutaneously. RBV and PegIFNα2a doses were adjusted to renal function, leukocyte, hemoglobin, and platelet levels, respectively, at the discretion of the treating physician.

Genotyping and quantification of HCV RNA

HCV genotyping was performed by reverse hybridization assay (Inno LiPA HCV II, Innogenetics, Gent, Belgium) [47]. Measurement of HCV RNA in serum was done by a quantitative reverse transcription polymerase chain reaction assay (COBAS TaqMan HCV Test 2.0, Roche Diagnostics GmbH, Mannheim, Germany [48]; lower level of quantification, 15 IU/ml) at baseline and therapy weeks 4, 12, end of treatment, and 4 as well as 12 weeks after end of treatment.

Statistical analyses

Unless indicated otherwise, all tests were two tailed and p values <0.05 were considered significant. Clinical and biochemical characteristics of patients were expressed as mean ± standard deviation (SD) or median, range as appropriate. Correlations between two variables were calculated by the spearman test. Furthermore, Chi-square, Fisher test, Kruskal-Wallis test, and Wilcoxon Mann-Whitney U test, were applied as appropriate.

Results

Patient characteristics

Thirty-five patients with chronic hepatitis C and advanced fibrosis (n = 7), cirrhosis Child-Pugh stage A (n = 16), and cirrhosis Child-Pugh stage B (n = 9) or C (n = 3) with or without hepatocellular carcinoma were treated with SOF based antiviral treatment regimens, including 8 patients after liver transplantation