Research Article

EASL JOURNAL OF HEPATOLOGY

The addition of a protease inhibitor increases the risk of infections in patients with hepatitis C-related cirrhosis

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Background & Aims: Antiviral therapy with interferon and ribavirin (double therapy) is associated with a significant risk of developing bacterial infections in patients with hepatitis C-related cirrhosis. The addition of telaprevir or boceprevir seems to increase this risk but there are no studies yet to compare the infection rate between both treatments. We aimed to assess rate, type and predictive factors of infection in cirrhotic patients undergoing triple or double antiviral therapy.

Methods: This was a retrospective analysis of prospectively collected data. 167 patients with hepatitis C-related cirrhosis undergoing triple therapy (cohort A) and 81 receiving double therapy (cohort B) were enrolled in the study. Only Child-Pugh A patients were included.

Results: The infection rate was significantly higher for patients in cohort A as compared to those in cohort B (25% *vs.* 9%, $p = 0.001$). Interestingly, respiratory tract infections were significantly more frequent in patients in cohort A (12% *vs.* 1%; $p = 0.049$). The use of triple antiviral therapy was the only predictive factor of infection. Severe infections were also more frequent in patients in cohort A, but the difference did not reach the level of significance (13% *vs.* 6%, $p = 0.123$).

Conclusions: Triple therapy carries a higher risk of infections in patients with cirrhosis and changes the pattern of infection in this subpopulation. Further studies are needed in order to establish the underlying mechanism of this event.

Keywords: Cirrhosis; Infections; Triple therapy.

Received 17 June 2014; received in revised form 4 September 2014; accepted 25 September 2014; available online 2 October 2014

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Abbreviations: HCV, hepatitis C; LT, liver transplantation; SBP, spontaneous bacterial peritonitis; SB, spontaneous bacteraemia; SVR, sustained virological response; CUPIC, compassionate use of protease inhibitors in viral C cirrhosis; HVPG, hepatic venous gradient pressure; SVR, sustained virological response; GMSF, granulocyte-monocyte stimulating factor; OR, odds ratio; GU, genitourinary; GI, gastrointestinal; NOD2, nucleotide-binding oligomerization domain-containing protein 2; TLR2, toll-like receptor 2; NSP, neutrophil serine proteases; NE, neutrophil elastase.

Introduction

Antiviral therapy with pegylated interferon and ribavirin is associated with an increased risk of serious adverse events in patients with hepatitis C (HCV)-related cirrhosis. Two studies have shown that HCV-positive patients with cirrhosis undergoing antiviral therapy, while on the waiting list for a liver transplantation (LT), exhibited a higher risk of bacterial infections as compared to non-treated patients [1,2]. Indeed, a case-control study by Carrion *et al.* [1] showed that patients receiving antiviral therapy before LT had a higher incidence of spontaneous bacterial peritonitis (SBP) and/or spontaneous bacteraemia (SB) as compared to untreated control patients waiting for a LT. This was particularly relevant for patients with severe liver dysfunction (Child-Pugh B or C), for whom the risk of bacterial infections was significantly increased as compared to Child-Pugh A patients. These results were recently confirmed by Everson *et al.* [2]. In this study, the authors found that 12% of the patients receiving antiviral therapy before LT developed bacterial infections as compared to none of the untreated patients.

The addition of a protease inhibitor (telaprevir or boceprevir) to pegylated interferon and ribavirin therapy (triple therapy) was a step forward in the treatment of hepatitis C [3–7]. Triple therapy significantly increased the chances of achieving a sustained virological response (SVR) in genotype 1 HCV-infected patients (even in more complicated patients, such as non-responders to a previous course of treatment and cirrhotics), becoming the standard of care in this subpopulation. However, results from real-life cohorts [8–11], conducted in patients with compensated cirrhosis, have shown that triple therapy is associated with serious adverse events in a non-negligible number of cases. The CUPIC study (Compassionate Use of Protease Inhibitors in viral C Cirrhosis) [8,9] was a multicentre cohort analysis performed in France to evaluate the efficacy and safety of triple antiviral

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therapy in treatment-experienced patients with compensated cirrhosis. Almost 50% of the patients developed serious adverse events during therapy, leading to early discontinuation of therapy in 21% of them. Infections were present in 5.5% of the patients and occurred after a median duration of antiviral therapy of 13.9 weeks. Age, albumin levels lower than 35 g/L and a platelet count lower than 100,000/mm^3 (a surrogate marker of portal hypertension) were independent predictors of the development of complications (including infections, decompensations of liver disease and death) during antiviral therapy. Similarly, Calleja *et al.*, found that an albumin level lower than 35 g/L and a bilirubin level greater than 2 mg/dl significantly increased the risk of serious adverse events (including infections and decompensations of liver disease) in a group of 170 patients with significant liver fibrosis (F3–F4), enrolled in the Spanish early access boceprevir program [10]. Another study performed by Rutter *et al.* [11] in patients with advanced fibrosis stage (F3–F4) found that 8% of the patients developed infections during triple therapy. Interestingly, none of the infections were SBP or SB, as commonly reported in patients with cirrhosis undergoing an interferon based antiviral therapy. Again, low albumin levels (<35 g/L) and the presence of portal hypertension (hepatic venous portal pressure gradient, HVPG >10 mmHg) were associated with the development of infectious complications.

Above mentioned data suggest that triple antiviral therapy in cirrhotic patients is associated with a significant risk of adverse events, especially infections. However, there are no studies comparing the rate and pattern of infections in patients with cirrhosis undergoing triple or double antiviral therapy. Therefore the aim of the current study is to compare the incidence and pattern of infections in patients with cirrhosis undergoing triple (either with telaprevir or boceprevir) or double antiviral therapy.

Methods

Study design

This is a retrospective cohort study performed in patients with HCV-related cirrhosis, treated with antiviral therapy between January 2000 and August 2013. Data were prospectively collected and all patients signed an informed consent. Four Spanish centres with experience in the management of antiviral therapies participated in the study (Hospital Clínic, Barcelona; Hospital Puerta del Hierro-Majadahonda, Madrid; Hospital Marqués de Valdecilla, Santander; and Hospital del Mar, Barcelona).

End points

The primary end point of the study was to compare the incidence of infections and grade 3/4 infections during antiviral therapy between patients treated with double therapy and patients receiving triple therapy with telaprevir or boceprevir. The secondary end point was to investigate type, pattern and predictive factors for the development of infections and grade 3/4 infections (severe infections) during antiviral therapy.

Patients

Two cohorts of patients were enrolled in this analysis. Cohort A was composed of 167 HCV-positive compensated cirrhotic patients, treated with triple antiviral therapy (pegylated interferon, ribavirin and a protease inhibitor) since 2012. Cirrhosis was diagnosed by the presence of F4 fibrosis (METAVIR) in a liver biopsy, portal hypertension (presence of oesophageal or gastric varices by an upper tract endoscopy, or an HVPG $\geqslant$6 mmHg), and/or a liver stiffness $\geqslant$14 kPa (measured by transient elastography). Cohort B was composed of 81 patients with HCV-related cirrhosis, receiving double antiviral therapy while on the waiting list for a LT. Indication for LT was hepatocellular carcinoma. All patients in this cohort were treated before 2012 when triple therapy was not available. Only Child-Pugh A patients were included in the study.

Treatment regimen

Patients in cohort A were treated with telaprevir (750 mg t.i.d or 1125 mg b.i.d), peginterferon α2a (180 μg/week) and ribavirin (dose adjusted by weight) or boceprevir (800 mg t.i.d), peginterferon α2b (1.5 μg/kg/week) and ribavirin (dose adjusted by weight). The type of protease inhibitor was at the discretion of the treating physician. Patients in cohort B were treated with peginterferon α2a (180 μg/week) or α2b (1.5 μg/kg/week) plus ribavirin (dose adjusted by weight). Doses and treatment regimens were administered according to the insert package for each drug. Patients in cohort B, received antiviral therapy when the estimated time to LT was 12 to 16 weeks. Sustained virological response was defined as undetectable HCV-RNA at week 12 after the end of therapy (either by completion of the therapy, discontinuation due to adverse events, or liver transplantation).

Adverse event definitions and dose adjustment

Anaemia was defined as a haemoglobin level $\leqslant$10 g/dl. Upon anaemia in cohort A, the ribavirin dose was decreased (200 mg each week until achieving the dose of 600 mg/d or directly to 600 mg/d according to the site) [12]. In the absence of improvement, an erythropoiesis-stimulating agent (erythropoietin or darbepoetin according to the site) was started. When haemoglobin levels decreased to a value $\leqslant$7 g/dl, or the patient developed anaemia-related symptoms a red-packed blood cell transfusion was indicated. In cohort B, anaemia management was performed as described in a previous study by Carrion *et al.* [1]. Neutropenia was defined as a neutrophil count $\leqslant$750/mm^3 and was initially managed with interferon dose reduction, according to the insert package and if there was no improvement, granulocyte-monocyte stimulating factor (GMSF) was added. Thrombocytopenia was defined as a platelet count $\leqslant$50,000/mm^3 and was controlled by reducing the peginterferon dose.

Infections

Infection was defined by the presence of symptoms and signs of infection that required local or systemic antibiotic treatment. Patients with fever (temperature $\geqslant$37.5 °C), local signs of infection and normal laboratory tests were managed in the outpatient clinic according to local protocols. If persistent fever (temperature $\geqslant$37.5 °C lasting more than 2 days after the last dose of interferon injection), leucocytosis, neutrophilia and/or deterioration of the clinical condition occurred, the patient was admitted to the hospital to discard the presence of infection. A detailed clinical history, physical examination, laboratory tests (including white blood cell count, fresh urine sediment and ascitic fluid cell count), chest-X ray, and blood and urine cultures were performed. Spontaneous bacterial peritonitis (SBP) was defined as the presence of $\geqslant$250 mm^3 polymorphonuclear cells in the ascitic fluid. Spontaneous bacteraemia (SB) was diagnosed on the basis of positive blood cultures in the absence of other sources of bacteraemia. Urinary tract infections, gastrointestinal infections, pneumonia and skin infections were diagnosed according to conventional criteria [1].

Grade 3 or 4 infections (severe infections) were defined according to the global severity index (GSI) grading scale of adverse events and laboratory abnormalities [13]. Briefly, grade 3 and 4 infections involve the presence of symptoms and signs of infection that require systemic antibiotic therapy and/or surgical intervention to treat the infection, a life-threatening infection (sepsis or septic shock) or an infection that led to a patient's death. Antibiotic treatment and support measures to treat moderate and severe infections were decided according to local protocols.

Statistical analysis

Differences between quantitative variables were analysed with parametric tests (Student's *t* test). Differences between qualitative variables were calculated using the χ^2 test. Demographic and analytical variables as well as the type of antiviral therapy (triple *vs.* double therapy) were analysed as possible predictive factors for the development of infections or grade 3/4 infections. Univariate analysis was performed introducing each variable in a logistic regression analysis. All variables with a p value <0.2 in the univariate analysis were introduced in a multivariate analysis, using a logistic regression model. Analysis was performed as intention-to-treat and patients in cohort A, who did not receive the protease