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12 weeks of interferon-based therapy is feasible in patients with hepatitis C-related cirrhosis and thrombocytopenia: A post hoc analysis of eltrombopag studies

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ABSTRACT

Background: A 24–48-week course of interferon-based therapy poorly tolerated in hepatitis C virus (HCV) cirrhosis patients with thrombocytopenia. Aim of the study was to identify patients at low-risk of liver-related complications over a 12-week course of interferon-based therapy.
Methods: We assessed the rate of complications and death during the first 12 weeks of interferon-based therapy in HCV cirrhotics with thrombocytopenia (platelets $\leq 75 \times 10^9$/L) enrolled in the ENABLE-1 and -2 phase 3 randomised controlled trials.
Results: Overall, among 1441 patients, 89 complications (6.9%) and 10 deaths (0.7%) were observed within the first 12 weeks of therapy. At univariate analysis baseline albumin levels and Model for End Stage Liver Disease (MELD) score ($\leq$35 g/L, $p < 0.001$, and $\geq$10, $p < 0.001$, respectively) were the only predictors associated with occurrence of complications and death. Of the 1026 patients with serum albumin >35 g/L (71.2%), one patient died (0.1%) and 17 experienced liver-related complications (1.7%). Among 667 patients with serum albumin >35 g/L and MELD score <10, no deaths occurred and 4 experienced liver-related complications (0.6%).
Conclusion: Among HCV cirrhotic patients with thrombocytopenia, albumin levels and MELD score can identify patients who may safely receive a 12-week course of interferon-based therapy with a low risk of complications.

1. Introduction

Cirrhotic patients chronically infected with hepatitis C virus (HCV) still represent the leading indication for liver transplant despite successful interferon-based therapy (IFN) certified by the achievement of sustained virological response (SVR) being associated with a reduction of liver-related events and hepatocellular carcinoma development [1–5]. However, poor tolerance and the limited number of patients who are eligible for IFN regimens limits effective treatment for chronic HCV infection [6,7].

The French CUPIC (Compassionate Use of Protease Inhibitors in Cirrhosis) and the eltrombopag studies identified a significant number of cirrhotic patients – in particular those with the co-existence of low platelets count ($<10 \times 10^9$/L) and albumin levels below 35 g/L – who, despite their urgent need of treatment, should not receive IFN due to its limited efficacy and poor tolerability [8]. Although new, all-oral IFN-free, direct antiviral agents are considered efficacious in the vast majority of HCV-infected patients, SVR data, obtained in studies carried out in subjects with advanced liver disease, are scanty [9,10]. Furthermore, these new antiviral agents were described to be of limited efficacy in cirrhotic infected by HCV genotype 3, still widespread worldwide at the highest risk of poor outcome [7,10–13]. Conversely, IFN combined with a short (12-week) course of sofosbuvir still represents to-date the most efficacious option to cure HCV genotype 3 patients with compensated cirrhosis who previously failed a full course of IFN [14–16].

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Eltrombopag to Initiate and Maintain Interferon Antiviral Treatment to Benefit Subjects with Hepatitis C-Related Liver Disease (ENABLE-1 and -2) are the largest phase 3 randomised controlled trials of chronic hepatitis C patients with compensated cirrhosis, severe thrombocytopenia (platelet count $<75 \times 10^9$/L) and portal hypertension [17]. Both studies evaluated the ability of eltrombopag, as a supportive treatment, to increase platelets to a level sufficient to initiate and maintain PEG-IFN/ribavirin antiviral therapy. Therefore, data from these studies permitted to achieve a comprehensive and reliable assessment concerning the incidence of hepatic decompensation and death during the treatment period in this subset of patients.

In the present post hoc analysis, we determined the rate of events that developed within the first 12 weeks of IFN treatment, as well as during the entire course of treatment and follow-up. Albumin levels and Model for End-stage Liver Disease (MELD) score were found to be associated with low risk of hepatic decompensation and death in the ENABLE studies at multiple logistic regression analysis for the entire period of the study [18]. We aimed to assess whether in these unique large cohorts of difficult-to-treat subjects with severe thrombocytopenia might be able to safely tolerate a short treatment duration period (12 weeks), to further guide physicians in daily practice.

2. Patients and methods

2.1. Patients

The ENABLE-1 and -2 were studies aimed at evaluating the ability of eltrombopag to initiate and maintain PEG-IFN and ribavirin treatment in thrombocytopenic patients with compensated chronic hepatitis C who were otherwise candidates to antiviral therapy. Briefly, all patients had received 24 (genotype 2 or 3) to 48 (genotype 1) weeks of IFN irrespective to the randomisation arm (eltrombopag or placebo). Inclusion and exclusion criteria, as well as the characteristics of the enrolled patients' cohorts, have been described elsewhere [17].

3. Methods

In the ENABLE trials, safety data were reviewed throughout the study by an independent data monitoring committee. After the completion of the studies, a blinded independent adjudication panel of external experts reviewed and adjudicated all events suggestive of hepatic decompensation. The methodology used to define clinical events is described in detail in Appendix A.

In the present study, all definite events of hepatic decompensation, infections and death that occurred within 12 weeks of initiation of antiviral therapy, during the entire study period, and during follow-up according to pre-established (see below) albumin and MELD cut-off, were reviewed. In addition, because it is not uncommon for cirrhotic patients to experience decompensation even if treatment is discontinued, in those patients who discontinued IFN during the first 12-week period any additional event attributable to IFN occurring within day 180 was also captured and included in the overall number of 12-week events. Albumin and MELD score cut-offs (3.5 and 10, respectively) were selected on the basis of their well-known, established and validated association with liver-related events in cirrhotic patients during IFN-based treatment [8,19,20]. Moreover, they were previously found to be independently associated with complications and death during the full-course of treatment and follow-up in the post hoc analysis carried out on the original study [18].

Table 1
Baseline characteristics of patients according to albumin levels.

	Albumin ≤35 g/dL *N* (%)	Albumin >35 g/dL *N* (%)	*p*
N	415	1026	
Age >40 years	396 (95.4)	942 (91.8)	0.017
Male gender	256 (61.7)	648 (63.2)	0.6
Bilirubin ≤0.7 mg/dl	9 (2.2)	108 (10.5)	<0.001
INR[a] ≤1.7	399 (96.6)	1001 (97.9)	0.2
HCV genotype[a] 2 or 3	149 (36.0)	297 (29.0)	0.01
Platelets <50,000/μL	146 (35.2)	257 (25.1)	<0.001
MELD score[a] <10	139 (34.0)	667 (66.0)	<0.001
Treatment			
PEG/RBV	140 (33.7)	346 (33.7)	1
PEG/RBV/ELT	275 (66.3)	680 (66.3)	

INR, international normalised ratio; PEG, pegylated interferon; RBV, ribavirin; ELT, Etrombopag.
[a] Some data are missing.

3.1. Statistical analysis

Continuous variables were categorised based on the pre-defined cut-off found to be associated (for the entire treatment duration) with the risk of hepatic decompensation and death [17]. Categorical variables are shown as absolute counts and proportions. Statistical analysis was carried out by means of Chi square test or Fisher's exact test. A p value <0.05 was considered significant. Univariate analysis to assess variable associated with hepatic decompensation and death during the 12-week course of treatment was carried out. Bilirubin and INR, which were previously found to be associated with the events at multivariate analysis during the full course of treatment [17], were not assessed since included in the MELD score and therefore considered as redundant variables.

4. Results

Baseline serum albumin level was available in 1441 patients while data to compute MELD score were available in 1420 patients (98.5%). Table 1 shows the baseline characteristics of patients enrolled in the ENABLE studies, subdivided according to albumin serum levels (≤35 g/L vs. >35 g/L). Males were 63% overall and 93% of patients were older than 40 years. As expected, patients with low levels of albumin had lower platelet count, higher MELD scores and bilirubin levels. HCV genotype 2/3 were more frequent in the low albumin level group.

Univariate analysis assessing variables associated with hepatic decompensation and death during the first 12-week course of treatment confirmed that albumin >35 g/L and MELD score <10 predict both events, while age, sex, and eltrombopag treatment, previously found being significantly associated with clinical outcomes during the full course of treatment [17], disappeared (Table 2).

Table 3 shows the number and rate of liver-related events within the first 12 weeks of therapy according to albumin levels and MELD score at baseline. Overall liver-related events, ascites, hepatic encephalopathy, pneumonia, infections and death were significantly higher in patients with albumin serum levels ≤35 g/L, while in those with MELD ≥10 only liver-related events, ascites, infections and death were significantly higher in comparison to those with MELD lower than 10.

Table 4 shows the number and rates of events in patients with albumin serum level >35 g/L and ≤35 g/L according to MELD score <10 vs. ≥10, respectively. In the subgroup of patients with higher baseline albumin levels patients with a baseline MELD score <10 had a significantly lower rate of liver-related events and ascites, as compared to patients with higher MELD scores. Of interest, for the