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Dual therapy with peg-interferon and ribavirin in thalassemia major patients with chronic HCV infection: Is there still an indication?

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ABSTRACT

Background: Iron overload and hepatitis C virus (HCV) infection together can lead to chronic liver damage in thalassemia major (TM) patients.
Aims: We investigated viral, genetic, and disease factors influencing sustained virological response (SVR) after peg-interferon and ribavirin therapy in TM patients with HCV infection.
Methods: We analyzed 230 TM patients with HCV infection (mean age 36.0 ± 6.3 years; 59.1% genotype 1; 32.2% genotype 2; 3.4% genotype 3; and 5.3% genotype 4; 28.7% carried CC allele of *rs12979860* in IL28B locus; 79.6% had chronic hepatitis and 20.4% cirrhosis; 63.5% naive and 36.5% previously treated with interferon alone) treated in 14 Italian centers.
Results: By multivariate regression analysis SVR was independently associated with CC allele of IL28B *SNP* (OR 2.98; CI 95% 1.29–6.86; $p = 0.010$) and rapid virologic response (OR 11.82; CI 95% 3.83–36.54; $p < 0.001$) in 136 genotype 1 patients. Combining favorable variables the probability of SVR ranged from 31% to 93%. In genotype 2 patients, only RVR (OR 8.61; CI 95% 2.85–26.01; $p < 0.001$) was associated with SVR higher than 80%. In 3 patients with cirrhosis a decompensation of liver or heart disease were observed. Over 50% of patients increased blood transfusions.
Conclusion: Dual therapy in TM patients with chronic HCV infection is efficacious in patients with the best virological, genetic and clinical predictors. Patients with cirrhosis have an increased risk of worsening liver or heart disease.

1. Introduction

Chronic liver disease is a common clinical issue in thalassemia major (TM) patients because iron overload and hepatitis C virus (HCV) infection together can lead to chronic liver damage [1,2]. In young patients free of HCV infection, adequate iron chelation prevents the development of liver fibrosis, but adult patients with active HCV infection frequently have severe liver fibrosis, even when they are undergoing regular and effective iron chelation therapy [3–5] and cirrhosis due to HCV infection is a major risk for development of hepatocellular carcinoma (HCC) and liver failure [6,7].

Antiviral therapy is indicated in TM patients with clinical evidence of significant liver fibrosis or cirrhosis [8]. The absence of cirrhosis, low iron hepatic concentration, and infection by HCV genotype other than 1b are the main clinical and virologic findings that predict a good response to therapy [9]. There is little data on the efficacy and tolerability of combination therapy with peg-interferon (PegIFN) and ribavirin (RBV) in TM patients since patients with hemoglobinopathies have been excluded from registration trials, and the addition of RBV therapy has long not been permitted in this subset of patients because of the high risk of severe hemolytic anemia [10,11].

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The primary aim of this analysis was to evaluate the efficacy and tolerability of combination therapy with Peg-IFN and RBV in a large number of TM patients with chronic HCV infection.

Secondarily, we investigated the role of HCV genotypes, single nucleotide polymorphisms (SNPs) located in and near the interleukin 28B (IL28B) locus, and iron overload on the efficacy of anti-HCV treatments. Finally, we evaluated the changes in blood transfusion regime and iron chelation therapy during the antiviral treatment.

2. Patients and methods

2.1. Selection of patients

We retrospectively analyzed TM patients with a diagnosis of chronic hepatitis C (CHC) treated with PegIFN/RBV in 14 Italian centers, beginning in 2009, when the Agenzia Italiana del Farmaco (AIFA) approved the use of RBV also for this subgroup of patients [12]. Therapy was indicated in adult patients with clinical or histological diagnosis of chronic hepatitis or compensated cirrhosis. Patients with decompensated liver disease (ascites, encephalopathy, bleeding from portal hypertension) or with hepatocellular carcinoma (HCC), patients with moderate or severe heart failure and/or cardiac arrhythmias that required therapy were excluded from antiviral treatment.

All patients signed an informed consent to record all clinical data and to store biologic samples for virologic and genetic tests.

2.2. Laboratory evaluation

All clinical and virologic data were recorded by single centers in a database. HCV genotyping was performed by INNO-LiPA HCV II assay (Innogenetics, Zwijndrecht, Belgium), and serum HCV-RNA was quantified by reverse transcription-PCR using Cobas Amplicor HCV Monitor Test, v 2.0 (Roche, Basel, Switzerland). The IL28B rs12979860 SNP (res 860) was genotyped using the TaqMan SNP genotyping allelic discrimination method (Applied Biosystems, Foster City, CA, USA).

Fibrosis stage was assessed histologically or through transient elastography (TE, Fibroscan®, Echosens, Paris, France). Cirrhosis was defined as F4 stage at liver biopsy according to the METAVIR or the Scheuer scores, or a TE value ≥12 kPa [13]. Biochemical and hematological parameters were recorded at baseline and at every blood transfusion. Serum HCV RNA was quantified at baseline, at week 4, at week 12, at the end of treatment (EOT), and 24 weeks after the EOT. A rapid virological response (RVR) was defined as HCV-RNA undetectable at week 4 of therapy and the sustained virological response (SVR), defined as undetectable HCV-RNA at week 24 post-treatment was considered to evaluate the efficacy of antiviral therapy.

Blood transfusion requirement 12 months before anti-HCV therapy as well as during and after treatment was recorded. Before the start of antiviral treatment, patients under treatment with deferiprone were withdrawn from treatment or switched to iron chelation therapy with deferoxamine or deferasirox to reduce the risk of neutropenia or agranulocytosis [14] during treatment with PegIFN/RBV.

2.3. Treatment schedules

Therapy was based on the combination of Peg-IFN apha2a (180 μg/week) or Peg-IFN alpha2b (1.5 μg/kg/week) in combination with RBV (15 mg/kg/day) for 48 weeks in genotype 1 or 4, and for 24 weeks in genotype 2 or 3.

2.4. Statistical analysis

All data were entered into a database and analyzed using SPSS 13.0 for Windows software (SPSS Inc., Chicago, IL, USA) on the intention to treat (ITT) basis. Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables as absolute and relative frequencies. The differences between continuous data were analyzed with the *t*-test, and corrected chi-square analysis was used for dichotomous or categorical variables. Fisher's exact test was used to examine the association between baseline features and SVR. Multiple logistic regression analysis was used to identify variables associated with SVR. The baseline variables included age, gender, serum levels of ALT and HCV RNA, HCV genotype, and IL28B *rs860* genotype. We also included RVR as an on-treatment variable associated with SVR. Variables with a threshold value of $p < 0.10$ at univariate analysis were included in the model, and variables with a threshold value of $p < 0.05$ were considered significant in the final model. Results are expressed as odds ratio (OR) and their 95% confidence intervals (CI).

3. Results

3.1. Baseline features

We analyzed data of 230 patients treated between September 2009 and December 2013. Their mean age was 36.0 ± 6.3 years, and 126 (54.8%) were male. One hundred and thirty-six (59.1%) patients were infected with genotype 1 (131 genotype 1b and 5 genotype 1a); 74 (32.2%) with genotype 2; 8 (3.4%) with genotype 3; and 12 (5.3%) with genotype 4. At baseline, median ALT was 51 IU/L (range 14–750) and median ferritin 655 ng/mL (range 19–7000). Baseline serum HCV-RNA was measured in 221 patients (96%), the median value was 552,943 IU/mL (range 193,000–17,700,000) and levels lower than 400,000 IU/mL were detected in 102 (46%) patients. The IL28B rs860 genotype was CC in 66 (28.7%), CT in 121 (52.6%) and TT in 43 (18.7%) patients. A liver biopsy was reported in the clinical history of 186 patients: 154 (79.6%) had a diagnosis of chronic hepatitis and 32 (20.4%) had a diagnosis of cirrhosis. A TE by Fibroscan was performed in all patients before to start antiviral therapy to reassess the degree of liver fibrosis. Eighty-nine patients (38.7%) had liver stiffness values lower than 7 kPa, 65 patients (28.3%) had values between 7 and 9 kPa, 29 (12.6%) patients had values between 9 and 12 kPa and 47 patients (20.4%) had values higher than 12 kPa. All 32 patients with a previous histological diagnosis of cirrhosis had liver stiffness values higher than 12 kPa. Evaluating the results of the TE 33% of patients had severe liver fibrosis, while 38% of patients had mild liver fibrosis.

One hundred and forty-six (63.5%) patients were naive to antiviral therapy, and 84 (36.5%) had previously received IFN monotherapy (33 patients with virologic relapse after the previous therapy and 51 non-responders). All patients received regular blood transfusions to maintain hemoglobin levels higher than 9 g/mL. Before starting antiviral therapy, patients were advised to switch from deferiprone as iron chelation therapy to reduce the risk of neutropenia. During antiviral treatment, 123 (53.4%) patients received deferasirox; 81 (35.3%) deferoxamine; 6 (2.6%) deferiprone; and 20 (8.7%) discontinued iron chelation therapy.

3.2. Effectiveness of treatment

Table 1 reports the baseline characteristics of patients according to viral genotype. Overall rates of SVR were 45.6%, 62.1%, 37%, and 42% in genotype 1, 2, 3 and 4 patients, respectively (Fig. 1).