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ORIGINAL ARTICLE

Reticulocyte production index as a predictor of clinically significant anemia in chronic hepatitis C patients receiving pegylated interferon combination therapy

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Summary *Background:* This work was conducted to study the relationship of reticulocyte production index to clinically significant anemia in chronic hepatitis C patients receiving pegylated interferon combination therapy.
Methods: A total of 69 chronic hepatitis C patients receiving pegylated interferon combination therapy were included. Clinically significant anemia was defined as a hemoglobin level of $<$ 10 g/dL. Reticulocyte count values were determined at the baseline and during treatment (4 weeks, 12 weeks, and 24 weeks). Reticulocyte production indices were calculated according to formulae. Clinical variables were analyzed using univariate analysis. Variables that were found to be significant on univariate analysis were included in multivariate analysis. A p value $<$ 0.05 was regarded as statistically significant.
Results: Clinically significant anemia was observed in 30 patients (43.5%), and 39 patients (56.5%) never developed clinically significant anemia during the whole treatment course. On multivariate analysis, age $>$ 60 years [odds ratio (OR), 2.94; 95% confidence interval (CI), 1.09–7.93], pretreatment hemoglobin level $<$ 14 g/dL (OR, 5.76; 95% CI, 2.01–16.48), and reticulocyte production index $<$ 0.9% (OR, 5.50; 95% CI, 1.78–16.97) at Week 4 were significantly associated with clinically significant anemia.

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Conclusion: Besides old age and low pretreatment hemoglobin level, our study showed that a reticulocyte production index < 0.9% at Week 4 was a significant factor associated with clinically significant anemia during pegylated interferon combination treatment.

Introduction

Combination therapy with pegylated interferon (PegIFN) and ribavirin can significantly improve sustained virological response (SVR) rate and is recommended in the treatment of patients with chronic hepatitis C [1,2]. However, patients receiving PegIFN combination therapy may develop severe anemia, which might lead to dose reduction, treatment discontinuation, and subsequent treatment failure [3]. A number of mechanisms are involved in the development of anemia, such as dose-dependent ribavirin-induced hemolysis [4] and/or interferon-induced bone marrow suppression [4,5]. Reticulocytes are red blood cells that have been recently released from the bone marrow, and a reticulocyte count is generally considered to be a measure of red blood cell production. However, in order to estimate the bone marrow response to anemia, the reticulocyte count should be adjusted to yield a reticulocyte production index (RPI) [6]. The aim of this study is to examine whether RPI can predict clinically significant anemia (CSA) in patients receiving PegIFN combination therapy.

Materials and methods

Patients

This study was conducted in a prospective manner from May 2011 to May 2012. All patients were anti-hepatitis C virus (HCV) antibody positive, had HCV RNA detectable in their serum by the polymerase chain reaction method, and showed elevated serum alanine transaminase (above the upper limit of the normal), serum hemoglobin (Hb) concentration > 12 g/dL, neutrophil > 1500/mm^3, and platelets > 10^5/mm^3 within 6 months prior to the treatment. Patients were excluded if they had baseline neutropenia (neutrophil count < 1500/mm^3), thrombocytopenia (platelet count < 10^5/mm^3), anemia (Hb level < 12 g/dL in women and < 13 g/dL in men), human immunodeficiency virus, hepatitis A or hepatitis B virus coinfection, decompensated liver disease, a serum creatinine level > 1.5 times the upper limit of normal, poorly controlled psychiatric disease, a recent alcohol or drug dependence, or substantial coexisting medical conditions. This study was approved by the Medical Ethics Committee of Chang Bing Show-Chwan Memorial Hospital, Changhua, Taiwan. Informed consent was obtained from each patient included in the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Treatment schedule

All patients were treated with PegIFN α-2a (PEGASYS; Roche, Basel, Switzerland) 180 μg subcutaneously once weekly or PegIFN α-2b (Pegintron; Schering-Plough, Kenilworth, NJ, USA) 1.5 μg/kg body weight subcutaneously once weekly, both in combination with oral ribavirin (Rebetol; Schering-Plough) at 1000—1200 mg/d dosed by body weight (< 75 kg, 1000 mg/d; > 75 kg, 1200 mg/d) for 24 weeks or 48 weeks. Patients with undetected HCV RNA at 4 weeks [rapid virological response (RVR)] received combination therapy for 24 weeks, whereas those without RVR received combination therapy for 48 weeks. Patients with an insufficient viral response at 12 weeks (detected HCV RNA with < 2—log10 decrease in HCV RNA from baseline) were considered to have treatment failure and discontinued therapy. Early virological response (EVR) was defined as undetected HCV RNA at 12 weeks of combination treatment. SVR was defined as undetected HCV RNA at 24 weeks after combination treatment. Ribavirin was given orally twice per day for the total dose. PegIFN was discontinued if the absolute neutrophil count was < 500/mm^3 or the platelet count was < 5.0 × 10^4/mm^3. When the patients' Hb dropped to < 10 g/dL, erythropoietin (EPO) 5000 U was injected subcutaneously per week. The patients were followed up at a 2-week interval. The ribavirin dose of 200 mg was reduced when the Hb concentration was still < 10 g/dL 2 weeks later. Ribavirin was discontinued when the Hb concentration decreased to < 8.5 g/dL, in accordance with the drug information for ribavirin [7]. The patients were divided into two groups: a CSA group and a non-CSA (without CSA) group.

Blood tests

All patients were examined for hematological and biochemical tests just prior to therapy, at the end of Week 2, Week 4, and every 4 weeks during the combination treatment. When the treatment was completed, the patients were assessed every 4 weeks up to 24 weeks after the end of treatment. HCV RNA levels were measured [screening visit (baseline); treatment Week 4, Week 12, Week 24, and Week 48; and follow-up Week 24] using the COBAS TaqMan assay (Roche Diagnostics, Indianapolis, IN, USA), with a lower limit of quantitation at 27 IU/mL. Genotyping of HCV was performed using a reverse hybridization assay (Inno-LIPA HCV II; Innogenetics N.V., Zwijnaarde, Belgium).