Antiviral Research 136 (2016) 37–44

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Effectiveness and safety of sofosbuvir plus ribavirin for HCV genotype 2 patients 65 and over with or without cirrhosis

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ARTICLE INFO

Article history:
Received 19 June 2016
Received in revised form
20 September 2016
Accepted 23 October 2016
Available online 24 October 2016

Keywords:
Hepatitis C virus
Gerontology
Cirrhosis
Sofosbuvir
Ribavirin
DAA

ABSTRACT

Older patients with chronic hepatitis C virus (HCV) infection have historically been designated difficult-to-treat. We evaluated the efficacy and safety of sofosbuvir (nucleotide NS5B polymerase inhibitor) plus ribavirin for patients with HCV genotype 2 infection in a real-world clinical setting, with the focus on elderly patients aged ≥ 65. This large, multicenter study consisted of 446 Japanese HCV genotype 2 patients (303 treatment-naïve and 143 treatment-experienced), including 190 (42.6%) aged ≥ 65 and 90 (20.2%) with compensated cirrhosis. Efficacy was assessed by the sustained virological response 12 weeks post-treatment (SVR12). The overall SVR12 rate was 95.7% (427/446), and the SVR12 rate of patients aged ≥ 65 was 95.3% (181/190). For treatment-naïve patients, almost all with compensated cirrhosis (95.6%, 43/45) achieved SVR12, irrespective of age. For treatment-experienced patients, cirrhosis undermined the treatment outcome, both for the aged ≥65 (SVR12: 80.0%, 20/25) and <65 (85.0%, 17/20) patient groups when compared to non-cirrhosis patients (≥65: 95.7%, 45/47 and < 65: 96.2%, 50/52). The most common adverse effect was anemia (hemoglobin <10 g/dL), especially for patients aged ≥ 65 with the inosine triphosphate pyrophosphatase CC genotype at rs1127354 (26.2%, 33/126). Notably, ribavirin reduction was not related to treatment failure. Only three (0.7%) patients, all aged ≥ 65, discontinued treatment, but all achieved SVR12. Sofosbuvir plus ribavirin for HCV genotype 2 was effective for patients aged ≥65, especially those who were treatment-naïve or treatment-experienced/non-cirrhosis.

Abbreviations: HCV, hepatitis C virus; PEG-IFNα, pegylated interferon alpha; DAA, direct-acting antiviral; ITPA, inosine triphosphate pyrophosphatase; eGFR, estimated glomerular filtration rate; IL28B, interleukin-28B; SNP, single nucleotide polymorphism; SVR, sustained virological response; RVR, rapid virological response; OR, odds ratio; CI, confidence interval.

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http://dx.doi.org/10.1016/j.antiviral.2016.10.012
0166-3542/

1. Introduction

Chronic hepatitis C virus (HCV) infection remains an important cause of morbidity and mortality worldwide (Thomas, 2013). The management of older patients is one of the main issues faced by clinicians because the proportion with liver cirrhosis or hepatocellular carcinoma rises with age (El-Serag, 2012; Ogawa et al., 2013a). Globally, genotype 2 accounts for only 13%, similar to genotype 4, but less than genotypes 1 and 3 (Gower et al., 2014). The prevalence of genotype 2 in African countries and East Asia is relatively high compared to Western countries.

Until recently, pegylated interferon alpha (PEG-IFNα) and ribavirin administrated for 24 weeks was the standard of care for patients with HCV genotype 2. However, the development of direct-acting antiviral agents (DAA) has provided effective IFN-free treatment regimens. The first-line treatment option in Western countries for patients infected with HCV genotype 2 has been the IFN-free combination of sofosbuvir plus ribavirin since 2014 (AASLD/IDSA HCV Guidance Panel, 2015; European Association for the Study of the Liver, 2015). Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase that is effective for the treatment of HCV genotype 2 when it is administrated in combination with ribavirin. Phase 3 trials have conducted efficacy and safety of this regimen for genotype 2 patients (Jacobson et al., 2013; Lawitz et al., 2013; Omata et al., 2014; Zeuzem et al., 2014; Ahn et al., 2016), however, there is a lack of sufficient information on older patients, especially for those aged 65 and over.

Higher age has been a major limitation of IFN-based treatment because of its poor tolerability, adverse effects, and poor antiviral response (Ogawa et al., 2012). Moreover, ribavirin has been associated with an increase in the development of anemia, especially for older patients and those with the inosine triphosphate pyrophosphatase (ITPA) CC genotype at rs1127354 (Ochi et al., 2010; Thompson et al., 2010; Ogawa et al., 2013b, 2015). Reduction of ribavirin due to hematologic and other toxic effects can have a negative effect on treatment outcome. Therefore, evaluation of this first-line regimen with sofosbuvir plus ribavirin, focused on older patients, will be useful for the management of patients with HCV genotype 2.

This multicenter, cohort study of chronic HCV genotype 2 patients treated with sofosbuvir plus ribavirin, including patients treatment-naïve and -experienced with or without compensated cirrhosis, was done in a real-world clinical setting to evaluate its effectiveness and safety, with the focus on patients aged ≥65.

2. Patients and methods

2.1. Patients

The Kyushu University Liver Disease Study (KULDS) Group consists of Kyushu University Hospital and its affiliated hospitals located in the northern Kyushu area of Japan. This multicenter cohort consisted of 458 consecutive Japanese patients who initiated a 12-week course of sofosbuvir (Sovaldi; Gilead Sciences K.K., Tokyo, Japan) (400 mg tablet once daily) and weight-based ribavirin (Rebetol; MSD K.K., Tokyo, Japan or Copegus; Chugai Co., Tokyo, Japan) between June and December 2015. Eligible patients were aged 20 years and older with confirmed chronic HCV genotype 2 infection. Exclusion criteria included (1) positivity for antibody to human immunodeficiency virus or positivity for hepatitis B surface antigen, (2) Child-Pugh B or C cirrhosis or a history of decompensated cirrhosis, (3) hemoglobin level < 11 g/dL at baseline, (4) estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 at baseline, (5) any non-HCV related liver disease, such as autoimmune hepatitis or primary biliary cholangitis, and (6) lost to follow-up. After exclusions, the data of 446 patients was available for analysis.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and STROBE statement. The study was approved by the Ethics Committees of Kyushu University hospital and each study site. Written informed consent was obtained from all patients before measurement of interleukin-28B (IL28B) and ITPA single nucleotide polymorphisms (SNPs).

2.2. Clinical, laboratory, and virological assessment

Clinical parameters were measured by standard laboratory techniques at a commercial laboratory (SRL Laboratory, Tokyo, Japan). Blood samples were obtained at baseline, weeks 1, 2, 4, 6, 8, and 12, then at 4 and 12 weeks after the end of treatment. Genotyping of the ITPA (rs1127354) and IL28B (rs8099917) genes were performed using the ABI TaqMan allelic discrimination kit (7500 Real Time PCR System; Applied Biosystems, Carlsbad, CA, USA). Liver cirrhosis was defined by liver biopsy demonstrating a METAVIR F4, transient elastography (FibroScan) of greater than 14.9 kPa (Ogawa et al., 2009) or an aspartate aminotransferase-to-platelet ratio index greater than 2 (Lackner et al., 2005), coupled with ultrasound examination with signs of cirrhosis (spleen size > 12 cm, portal vein >16 mm, or nodules within the hepatic parenchyma). These assessments were performed within one month before the initiation of antiviral treatment.

HCV RNA was measured using real-time reverse transcriptase PCR assay (COBAS TaqMan HCV assay version 2.0) (Roche Diagnostics, Tokyo, Japan), with a lower limit of quantitation of 15 IU/mL and an outer limit of quantitation of 6.9×10^7 IU/mL (1.2–7.8 log IU/mL referred to $\log_{10}$ IU/mL). Sustained virological response (SVR) 12 was categorized as undetectable HCV RNA (target not detected) at week 12 after the end of treatment, and rapid virological response (RVR) was categorized as undetectable HCV RNA at week 4.

2.3. Ribavirin dose adjustments

Ribavirin was given orally at a daily dose of 600–1000 mg based on body weight. Ribavirin adjustment due to anemia was done at the discretion of the physicians at each hospital. In principle, when hemoglobin decreased to <10.0 g/dL, the ribavirin dose was reduced by 400 mg for patients receiving 600 or 800 mg and by 600 mg for those receiving 1000 mg. If hemoglobin decreased to <8.5 g/dL, ribavirin was discontinued transiently. If ribavirin was withheld due to severe anemia or rash, an attempt could be made to restart it at 400 mg daily and further increase the dose to 600 mg daily when the symptoms decreased. Erythropoietin use was not allowed during treatment, but blood transfusion was done when necessary.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS Statistics version 22.0 (IBM SPSS Inc, Chicago, IL, USA). Baseline continuous data are expressed as median (first-third quartiles) and categorical variables are reported as frequencies and percentages. Univariate analyses were done using the Chi-square, Fisher's Exact, Student's *t*, or Mann-Whitney U tests as appropriate. Variables with $P < 0.05$ in univariate analysis were evaluated using multivariable logistic regression to identify variables significantly associated with SVR12. The results are expressed as odds ratios (OR) and their 95% confidence interval (CI). A *P* value less than 0.05 was regarded as statistically significant in all analyses.