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Effectiveness and safety of community-based treatment with sofosbuvir plus ribavirin for elderly patients with genotype 2 chronic hepatitis C

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ABSTRACT

Background: The aim of this study was to clarify the effectiveness and safety of sofosbuvir/ribavirin therapy for elderly patients with genotype 2-infected chronic hepatitis C (CHC) in Japan.
Methods: A multicenter, retrospective study evaluated the effectiveness and safety of sofosbuvir/ribavirin based on real-world clinical data.
Results: The subjects consisted of 270 patients, 47.0% of whom were aged ≥65 years. The sustained virological response rates in patients aged <65 and ≥65 years were 98.6% and 95.3%, respectively. Hemoglobin levels decreased during treatment due to ribavirin-related hemolysis, and were significantly lower in patients aged ≥65 years than those aged <65 years at all time-points. A reduction in ribavirin dose was necessary in 31.0% (26/84) of patients with hemoglobin levels <13.0 g/dL and in 70.7% (39/127) of those aged >65 years. Although the most frequent adverse event was anemia, no patients discontinued the use of either ribavirin or sofosbuvir. The incidence of ribavirin-related anemia in patients aged ≥65 years was 34.6% and significantly higher compared with that in patients aged <65 years (2.8%).
Conclusions: Treatment with sofosbuvir/ribavirin for genotype 2-infected CHC was effective and safe even for elderly patients, although the incidence of adverse events including ribavirin-related anemia was relatively high.

1. Introduction

It has been reported that there are 123 million chronic hepatitis C (CHC) patients around the world, and the prevalence rate is approximately 2% [1,2]. Genotype-2 CHC patients account for approximately 13% of these cases worldwide but for 34.2% in Japan [1]. Although pegylated-interferon/ribavirin therapy yields a high efficacy rate [3–6], the therapy causes various adverse events and, therefore, is not tolerated or contraindicated for some patients [7]. In particular, elderly patients have a higher likelihood of reduced dosing and/or premature discontinuation of treatment due to low tolerability and high incidence of adverse events [8–11]. Because Japan is a super-aged society, where more than 21% of the population is ≥65 years old, as defined by the World Health Organization, CHC patients in Japan are older compared with those in other regions and countries [12–14]. An anti-hepatitis C virus (HCV) agent with high efficacy and safety is urgently needed for such elderly patients.

In the treatment of CHC, direct-acting antivirals (DAAs), which are oral drugs, are taking the place of interferon-based treatments and becoming first-line agents [15,16]. In several clinical trials in patients with genotype 2 CHC [17–20], sofosbuvir/ribavirin had high efficacy and a low incidence of adverse events in comparison with pegylated-interferon/ribavirin: the sustained virological response (SVR) rate was 86–97%, the incidence of severe adverse

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events was low (1–8%), and the rate of treatment discontinuation was 0–4% [17]. Currently, the American Association for the Study of Liver Diseases (AASLD) guidelines recommend sofosbuvir and ribavirin combination therapy for patients with genotype 2 CHC [15]. In addition, The Japan Society of Hepatology (JSH) recommends sofosbuvir/ribavirin as first-line treatment [16]. However, the mean age of patients enrolled in the clinical trials was about 48–58 years, which was relatively young, and the maximum age was 75 years [17–20]. As described above, patients with CHC in Japan, a super-aged society, have a more advanced age than the rest of the world [12–14]. Indeed, the HCV antibody-positive rate in the early 2000s was approximately 1% or less in patients aged <60 years, whereas it exceeded 3% in those aged ≥60 years [12–14]. Therefore, in Japan, the median age and the maximum age of patients who received community-based anti-HCV treatment were 63–64 years and 82 years, respectively [21,22]. In elderly patients with unfavorable factors, such as low tolerability and poor treatment response, the effectiveness and safety of DAA-based treatment have not yet been fully clarified.

The aim of this study was to evaluate the effectiveness and the safety of community-based sofosbuvir plus ribavirin combination therapy for genotype 2-infected CHC patients in a real-world super-aged society.

2. Patients and methods

2.1. Patients

Between June 2015 and February 2016, patients chronically infected with HCV genotype 2 were enrolled in this study at six specialized centers: Nippon Medical School Chiba Hokusoh Hospital (Inzai, Japan), Shinmatsudo Central General Hospital (Matsudo, Japan), Jikei University School of Medicine (Tokyo, Japan), Otakanomori Hospital (Kashiwa, Japan), Nagoya City University Graduate School of Medical Sciences (Nagoya, Japan), and Nippon Medical School (Tokyo, Japan). Patients received sofosbuvir/ribavirin therapy as described below. Leading inclusion criteria were as follows: (1) CHC that was diagnosed by laboratory, virology, and histology findings; (2) HCV genotype 2 confirmed by the conventional polymerase chain reaction (PCR)-based method or chemiluminescence enzyme immune assay (BML, Tokyo, Japan); (3) serum HCV RNA levels of >1.2 log IU/mL, as determined by quantitative analysis with real-time PCR (4) 20 years of age or over; and (5) hemoglobin concentration >9.0 g/dL. Leading exclusion criteria included (1) decompensated liver cirrhosis (Child–Pugh class B or C); (2) pregnancy or lactation (3) concurrent treatment with any contraindicated drugs; (4) hypersensitivity to ribavirin and sofosbuvir; and (5) eGFR values of <30 mL/min/1.73 m^2. Compensated liver cirrhosis was defined as biopsy-proven cirrhosis (Metavir score = 4), computed tomography and/or ultrasonography with Child–Pugh class A. Sample size was determined by exceeding the number of patients analyzed in a phase 3 trial in Japan [20]. This study was designed according to the ethical guidelines of the Helsinki Declaration in 2013, and was approved by the Ethics Committee of each participating institution (registration UMIN000018453). Written informed consent was obtained from all patients before entry into the study.

2.2. Treatment protocol

Patients received an oral dose of 400 mg sofosbuvir (SOVALDI, Gilead Sciences K K., Tokyo, Japan) once a day, and oral ribavirin (REBETOL; MSD, Tokyo, Japan, or COPEGUS; Chugai, Tokyo, Japan) was taken twice a day and the dose was adjusted by body weight (600 mg, 800 mg and 1000 mg per day for <60 kg, 60–80 kg, and >80 kg, respectively) based on the guidelines of the Ministry of Health, Labor and Welfare of Japan. Ribavirin doses were appropriately reduced when an adverse event such as anemia occurred during the treatment course. The treatment period was 12 weeks. Physical, hematological, and biochemical examinations were performed at entry into the study, at the start of treatment, at 2-week intervals during treatment, and then every month during the 12-week follow-up period after the completion of treatment.

2.3. Laboratory tests

Serum HCV RNA levels were measured using a real-time PCR-based method (COBAS TaqMan HCV Test 2.0; Roche Diagnostics, Tokyo, Japan). The lower detection and quantification limit was 1.2 log IU/mL. eGFR values were calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × creatinine (mg/dL)$^{-1.094}$ × age (years)$^{-0.287}$ (×0.739 for females). The single nucleotide polymorphism (SNP) rs8099917 near the *IFNL3* gene was determined by real-time PCR using a TaqMan® SNP genotyping assay (Life Technologies, Foster City, CA). rs8099917 SNP genotypes were classified into two categories: TT and non-TT (TG or GG). SNPs at rs1127354, which is located in the locus adjacent to the inosine triphosphatase (*ITPA*) gene, were also genotyped by real-time PCR. rs1127354 SNP genotypes were classified into two categories: CC and non-CC. FIB-4 index, an index marker for the degree of liver fibrosis, was determined using the formula: age ([yr] × AST [U/L])/[(PLT [10^9/L]) × (ALT [U/L])$^{1/2}$)] (ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelets). FIB-4 index >3.25 was defined as advanced liver fibrosis.

2.4. Definition of treatment responses

When serum HCV RNA was undetectable at 4 weeks of treatment, patients were regarded as having a rapid virological response (RVR). When serum HCV RNA was undetectable at the completion of treatment, patients were judged as having an end of treatment response (ETR). When serum HCV RNA was undetectable at 24 weeks after the completion of treatment, patients were considered to have achieved SVR.

2.5. Statistical analysis

Fisher's exact test was performed in order to compare virological response rates according to baseline factors. Wilcoxon signed-rank test was performed to analyze the transition of hemoglobin levels. Logistic regression analysis for univariate comparison was performed to investigate whether each factor influenced SVR. Multiple logistic regression analysis was also performed to identify significant, independent factors for achieving SVR. A P value of <0.05 was regarded as significant. We used SPSS version 17.0 software (IBM Japan, Tokyo, Japan).

3. Results

3.1. Background

We analyzed 270 patients who were selected in accordance with the inclusion and exclusion criteria. The baseline patient characteristics are shown in Table 1. They consisted of 131 females and 139 males, with a median age of 63 years (range, 25–89 years). Patients aged <65 and ≥65 years accounted for 53.0% (143/270) and 47.0% (127/270), respectively. Baseline hemoglobin levels were 13.9 g/dL (range, 9.1–18.3) for all patients, 14.5 g/dL (range, 11.4–18.3) for those aged <65 years, and 13.0 g/dL (range, 9.1–17.2) for those aged ≥65 years, indicating that baseline hemoglobin levels decreased significantly with age ($P = 5.13 \times 10^{-12}$). Overall, patients