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Original

The efficacy and safety of elbasvir and grazoprevir for hepatitis C virus genotype 1 in a real clinical setting

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Abstract

We aimed to evaluate the efficacy and safety of 12-week treatment with elbasvir (EBR) and grazoprevir (GZR) in patients with hepatitis C virus (HCV) genotype (GT) 1 infection in a real-world setting.

A total of 67 patients with chronic hepatitis or compensated hepatic cirrhosis and GT 1 HCV infection were treated with EBR + GZR for 12 weeks and followed for 12 weeks after the completion of treatment. A sustained virological response (SVR12) was defined as undetectable HCV RNA 12 weeks after completing treatment. The efficacy and safety of this 12-week treatment regimen were analyzed.

Among the 67 patients (male, n=39; female, n=28), 23 (34%) had compensated liver cirrhosis, while only 1 (1%) had experienced treatment failure with another DAA treatment regimen. The overall SVR12 rate was 97% (95% confidence interval 0.896 – 0.996), and the rate was not significantly affected by age, sex, liver stiffness, Fib-4 index, or eGFR at baseline. No severe adverse events occurred. The most frequent adverse event was increased alanine aminotransferase concentration in 4 patients (6%).

The efficacy and safety of 12 weeks of EBR+GZR for patients with chronic hepatitis or compensated hepatic cirrhosis and HCV GT 1 infection was confirmed in this study.

Key words: *elbasvir/grazoprevir, hepatitis C virus, genotype 1*

I. Introduction

Patients with hepatitis C virus (HCV) infection are at risk of progressive liver disease, which ultimately leads to cirrhosis and hepatocellular carcinoma [1)]. The HCV genotype (GT) 1 is the major type in Japan and is resistant to interferon (IFN)-based treatment. However, since 2014, several all-oral IFN-free drugs, direct-acting antivirals (DAA), have been launched in Japan. Although nonstructural protein (NS) 5A resistance-associated substitutions (RAS) reduce decline the efficacy of treatment, DAAs have achieved safe and satisfactory outcomes in HCV GT 1, and have become the standard treatment in Japan. Thus, the elimination of HCV has become more important.

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Combination treatment with the NS5 inhibitor elbasvir (EBR), plus the NS3/4A protease inhibitor grazoprevir (GZR) for HCV GT 1 or GT 4 has been approved for use in Japan since 2016. In a Japanese phase III trial, the rate of HCV elimination was 96.5% in patients with chronic hepatitis, and 97.1% in patients with cirrhosis [2]. Moreover, EBR + GZR treatment can be given to patients with renal dysfunction [3]. Thus, in this study, we assessed the efficacy and safety of 12-week treatment with EBR + GZR in patients with chronic hepatitis or compensated hepatic cirrhosis among those with chronic HCV GT 1 infection, including some patients with renal dysfunction, in an actual clinical setting.

II. Methods

1. Patients

This study was a retrospective cohort study. Consecutive patients with chronic HCV GT 1 infection who had chronic hepatitis or compensated hepatic cirrhosis were treated with EBR+GZR for 12 weeks between December 2016 and August 2020 at Iwate Medical University Hospital and an affiliated institution. The inclusion criteria were as follows; age ≧ 20 years, serum HCV RNA concentrations > 1.2 log IU/mL at the time of screening, and confirmation of chronic HCV GT 1 infection before treatment. The presence of cirrhosis was investigated at screening according to various combinations of liver biopsy findings, Fib-4 index ≧ 3.25, serum fibrosis markers, transient elastography, and liver imaging examination (ultrasonography, computed tomography, or MR imaging), as well as the patient's clinical state. The following exclusion criteria were applied: HCV GT other than 1, decompensated hepatic disease (Child–Pugh grade B or C), other causes of liver disease, acute and chronic hepatitis B virus (HBV) infection, and human immunodeficiency virus infection.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Iwate Medical University (approval number H28-159) and the relevant committees at the treatment site. Written informed consent was obtained from each participant before therapy.

2. Treatment protocol

Patients received 50 mg of EBR (Erelsa®, MSD co., Itd., Japan, Tokyo) plus 100 mg of GZR (Grazyna®, MSD co., Itd., Japan, Tokyo) orally once daily for 12 weeks and were followed for 12 weeks after completing treatment. There was no financial support from MSD co., Idt.

The final decision to reduce the dose or discontinue treatment was made by the attending physicians.

3. Laboratory tests

Peripheral blood samples were obtained at baseline, 4 weeks after the first administration of EBR + GZR, and every 4 weeks thereafter until 24 weeks. Serum HCV RNA levels were measured by the COBA TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The detection range of this quantitation assay ranges from 1.2 - 7.8 log IU/mL (15 - 6.9 × 10^7 IU/mL), and undetectable HCV RNA is defined as negative. HCV GT was determined by PCR according to the method of Okamoto et al. [4].

To evaluate the effect of baseline NS5A RAS in patients with HCV GT1, NS5A amino acid positions 31 and 93 were assessed by

direct sequencing and NS5A Y93 mutations at baseline were evaluated by Cycleave PCR (SRL Laboratory, Tokyo, Japan).

Normal alanine aminotransferase (ALT) concentration was defined as an ALT level of less than 30 U/L. Estimated glomerular filtration rate (eGFR) was calculated by entering the required information into the following formula: eGFR (mL/min/1.73 m^2) = 194 × [creatinine (mmol/L) × 0.01] $^{-1.094}$ × age (years) $^{-0.287}$ (× 0.739, if female). Chronic kidney disease (CKD) was classified according to the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for CKD [5]. We further stratified the patients into three groups according to their eGFR at baseline, as follows: stage 1/2 (eGFR ≧ 60 mL/min/1.73 m^2); stage 3 (eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2); and stage 4/5 (eGFR < 30 mL/min/1.73 m^2).

4. Treatment efficacy and safety

A sustained virological response (SVR) was defined as undetectable HCV RNA 12 weeks after completing treatment. A non-SVR was defined as detectable HCV RNA at the end of treatment, or undetectable HCV RNA at the end of treatment but detectable HCV RNA 12 weeks later. The primary efficacy endpoint was the percentage of patients who achieved an SVR12 in the intention-to-treat (ITT) analysis.

Treatment-associated adverse events (AEs), including clinical, biochemical and hematological abnormalities, that occurred during this study were reported and collected. The frequency of treatment-associated AEs was also calculated. AE grade conformed to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The primary safety endpoint was the frequency of AEs.

5. Statistical analyses

The treatment outcomes were analyzed on an ITT basis. In this study, we defined the subjects for ITT as all patients who received at least one dose of the study drug (ITT included cases of nonvirological failure [e.g., loss of follow-up or early discontinuation]). The 95% confidence interval (CI) was calculated for the rapid virological response (RVR [defined as undetectable HCV RNA 4 weeks after the initial treatment]), the end of treatment (EOT) and the SVR12 rate. Categorical variables were analyzed using the chi-squared test and Fisher's exact test and continuous variables were analyzed using the Friedman's test to compare the clinical parameters in the subgroup. P-values of <0.05 (as determined by a 2-tailed test) were considered statistically significant. However, statistical significances of difference among the three subgroups were decided using Bonferroni correction. The statistical analyses were performed using the SPSS software package (SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA).

III. Results

1. Patient characteristics

A total of 67 (male, n=39; female, n=28) chronic HCV-infected patients were enrolled in this study. The patients' baseline characteristics are showed in Table 1. The median age was 67 years (range, 32–83 years), and the median HCV RNA concentration at baseline was 5.9 log IU/mL (range, 2.9–7.1 log IU/mL). Patients with a Fib-4 index of ≧ 3.25 accounted for 46% of the study population (31/67), and 34% (23/67) had clinical

Table 1. Baseline characteristics

Parameters	N=67
Age*	67 (32-83)
Gender [male/female]	39/28
Body Mass Index (kg/m^2) *	22.9 (14.4-32.1)
White Blood Cell ($/\mu L$) *	4590 (1530-7410)
Hemoglobin (g/dL) *	12.9 (9.0-16.7)
Platelets ($\times 10^4/\mu L$) *	14.6 (4.4-44.2)
Albumin (g/dL) *	4.0 (2.9-4.9)
Total bilirubin (mg/dL) *	0.6 (0.2-1.6)
AST (U/L) *	35 (12-164)
ALT (U/L) *	33 (13-204)
eGFR ($mL/min/1.73m^2$)	69 (9.2-90)
CKD stage [1-2/3/4-5]	48/17/2
AFP (ng/mL) *	5.1 (1.3-731.0)
HCV RNA (Log IU/mL) *	5.9 (2.9-7.1)
HCV genotype [1/2]	67/0
NS5A Y93 RAS [absence/presence/unknown]	62/4/1
NS5A L31 RAS [absence/presence/unknown]	64/2/1
Chronic hepatitis / Liver cirrhosis	44/23
Fib-4 index [<3.25/ ≧ 3.25]	36/31
Treatment history of HCV [Yes/No]	1/66
Treatment history of HCC [Yes/No]	11/56
Anti-HBc antibody positive [positive/negative]	25/37

* Date are expressed as median (range)
AST, Asparates aminotransferase; ALT, Alanine aminotransferase; AFP, Alfa-fetoprotein; HCV, hepatitis C virus; RAS, resistance-associated substitutions; HCC, hepatocellular carcinoma.

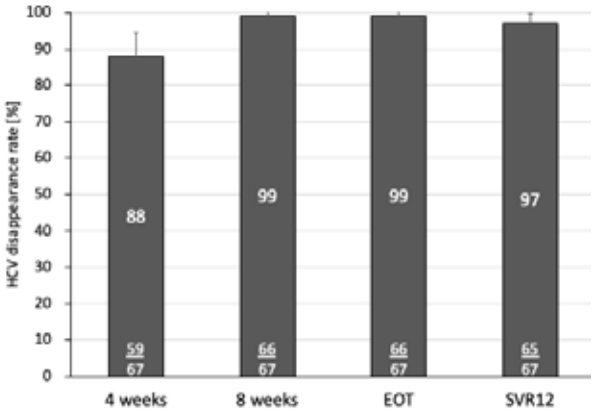

Fig. 1. The rate of HCV RNA disappearance over time. The rate of HCV RNA disappearance were 88%, 99% and 99% at 4, 8 and 12 weeks, respectively, after initiating EBR + GZR treatment. The overall SVR rate was 97%. The ratio of response number to total number was shown in the bottom of the each bar graph. The error bar indicates the 95% confidence interval.
HCV, hepatitis C virus; EBR, elbasvir; GZR, grazoprevir; SVR, sustained virological response; EOT, end of treatment.

compensated cirrhosis. The median eGFR at baseline was 68.8 mL/min/1.73 m^2 (range, 9.2–90.0 mL/min/1.73 m^2), and 11 patients (16%) had a history of therapy for HCC. Only one patient had a history of previous DAA treatment (asunaprevir; NS3/4A protease inhibitor / daclatasvunr; NS5A inhibitor). Double mutation of NS5A Y93 and L31 was not detected, and the existence of NS5A RAS Y93 or L31 at baseline was observed in six patients (9%).

2. Efficacy

The overall SVR rate and HCV disappearance rate over time are shown in Figure 1. The results revealed that the RVR rate was 88% (95% CI 0.778 – 0.947), the EOT rate was 99% (95% CI 0.920 – 1.000), and the

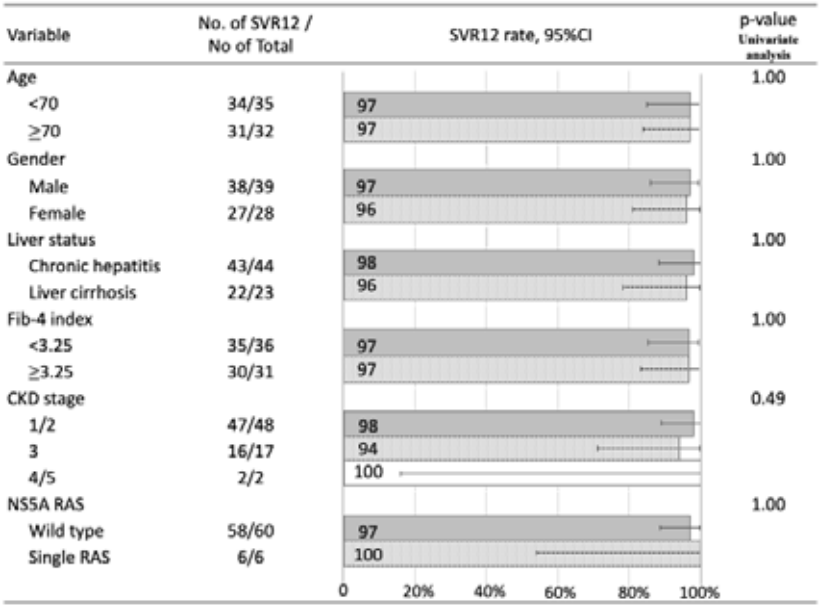

Fig. 2. The SVR rate according to age, sex, liver status, Fib-4 index, CKD stage, and NS5A RAS at baseline.
The SVR was not significantly associated with age, sex, liver status, Fib-4 index, CKD stage, or NS5A RAS.
SVR, sustained virological response; Fib-4, fibrosis-4; CKD, chronic kidney disease; RAS, resistance-associated substitution; CI, 95% confidence interval.

overall SVR12 rate was 97% (65/67) (95% CI 0.896 – 0.996); however, two patients were lost to follow-up. We also analyzed the factors associated with an SVR. The SVR rates, stratified according to age, sex, liver status, Fib-4 index, CKD stage, and NS5A RAS at baseline are shown in Figure 2. There were no significant associations between the SVR rate and age, sex, liver status, Fib-4 index, CKD stage, or NS5A RAS.

3. Safety

ALT concentration elevated to more than 3 times the upper limit of the normal range in four patients (6%), and on average, the increase occurred 7 weeks (4–12 weeks) after starting the medication. One patient discontinued treatment, two patients received a reduced dosage of GZR, and one patient continued treatment because elevation of ALT concentration was observed just before the EOT. The ALT concentrations of the four patients with increases returned to the normal range, and all four patients achieved an SVR.

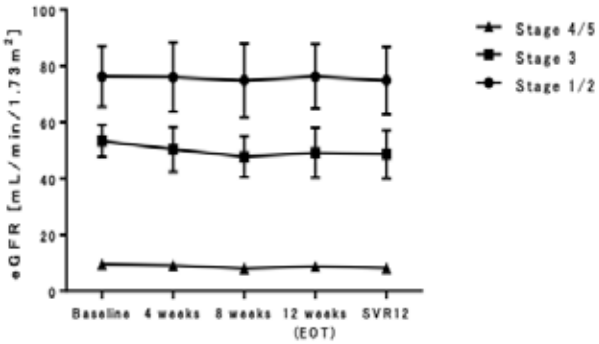

Fig. 3. The change in eGFR from baseline to SVR12 according to CKD stage.
There was no significant change between baseline and SVR12 according to CKD stage. The error bar indicates the standard deviation.
eGFR, estimated glomerular filtration rate; SVR12, sustained virological response 12 weeks after treatment; CKD, chronic kidney disease; EOT, end of treatment.

No other noticeable AEs were recorded. The change in eGFR between baseline and SVR12 did not differ according to the stage of CKD (Fig. 3).

IV. Discussion

In the present study, the RVR rate was 88%, the EOT rate was remarkably high as 99%, and the SVR rate was 97%. The treatment efficacy of EBR + GZR in a real clinical setting was as good as that in a clinical trial. Several reports have evaluated the factors influencing the treatment efficacy of EBR + GZR [6-8]. These studies reported that a history of previous IFN-free DAA treatment and double mutation in NS5A RAS Y93 and L31 influenced treatment efficacy. However, in this present study, only one patient who had previously experienced treatment failure with another IFN-free DAA treatment received EBR + GZR, and we identified no patients with double mutation of NS5A Y93 and L31. Thus, we did not identify factors influencing treatment efficacy in the present study.

This treatment was safe and well-tolerated. We did not observe fatigue or headache as treatment-associated AEs, in this study. The most frequent AE in patients receiving this treatment was increased ALT. On average, increased ALT occurred 7 weeks after starting the medication, and patients were asymptomatic. Therefore, patients' hepatic function should be monitored throughout the course of treatment. The risk of increased ALT concentration is linked to the GRZ concentration. In this study, owing to increased ALT, one patient discontinued treatment, two patients received a reduced dosage of GZR, and one patient continued treatment because elevation of ALT concentration was observed just before the EOT. In all four of these patients, ALT concentration returned to the normal range. Of note, the Japan Society of Hepatology states in its guidelines concerning the management of hepatitis C virus infection that patients with a history of HBV infection must be carefully monitored for HBV reactivation during treatment for HCV [9].

In this study, the proportion of anti-HBc antibody-positive patients was 40% at baseline. Three of four patients with elevated ALT levels were anti-HBc antibody-positive. However, their ALT levels recovered with drug reduction, cessation and observation, so we concluded that HBV reactivation had not occurred.

The proportion of EBR and GRZ excreted through the kidneys is < 1%, and it is not necessary to adjust the dose of EBR and/or GZR, even in patients with impaired kidney function. The results of the C-SURFER clinical trial confirmed the high degree of safety and therapeutic effect of EBR + GRZ in HCV patients with comorbid stage 4 or 5 kidney impairment [10].

Furthermore, several reports in Japan have demonstrated the high treatment efficacy and safety of 12-week EBR+GZR treatment in patients with CKD stage 4 or 5 and in hemodialysis patients [6, 11]. In the present study, efficacy of the treatment was high, regardless of the CKD stage. Furthermore, patients with poor renal function showed no treatment-associated AEs. There was no significant change between baseline and SVR12 according to CKD stage. The Japan Society of Hepatology recommends EBR + GZR when treating GT 1 chronic hepatitis C patients

with CKD [9].

The present study has some limitations. First, due to its retrospective design, there might have been bias in candidate selection, such as with or without NS5A RAS, or a history of previous DAA treatment. Second, because the non-SVR rate was extremely low, we could not fully analyze the factors associated with treatment failure. Third, RAS was analyzed only at NS5A Y93 and L31.

In conclusion, in this real-world clinical study, 12-week EBR + GZR treatment was effective and safe for patients with HCV GT 1 infection who had chronic hepatitis or compensated hepatic cirrhosis.

This treatment eliminates HCV at a very high rate, which is of substantial benefit for treated patients. However, HCC developed even in one patient with an SVR, and several risk factors have been identified for HCC occurrence after DAA treatment; namely, older patients, and those with liver cirrhosis, diabetes mellitus, previous HCC history, or alcohol abuse [12]. Therefore, surveillance for HCC is recommended, including in these high-risk patients.

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Conflicts of interest: The authors have no conflict of interest to declare.

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実臨床における Genotype 1 型 C 型肝炎に対する エルバスビル・グラゾプレビルの治療効果と安全性

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要旨

C 型肝炎ウイルス遺伝子型 1 型に対するエルバスビルとグラゾプレビルによる 12 週間治療の有効性と安全性を実臨床で評価する目的で 67 人の C 型肝炎ウイルス遺伝子型 1 型慢性肝炎または代償性肝硬変患者をエルバスビルとグラゾプレビルにて 12 週間治療後 12 週間追跡した．治療終了後 12 週の時点で HCV RNA が検出されない場合を SVR12 と定義し，この 12 週間治療の有効性と安全性について解析した．その結果 67 人（男性 39 人，女性 28 人）がこの治療を受けた．このうち 23 人（34％）が代償性肝硬変で，1 人のみ（1％）が以前に他の DAA 治療を受けたが非 SVR であった．全体の SVR12 率は 97% (95％信頼区間 0.896 – 0.996) であった．SVR12 は治療開始時の年齢, 性別, 肝硬度，Fib-4 index，CKD ステージによる影響を受けなかった．重篤な有害事象も発生しなかった．ALT 値の上昇が最も多い有害事象で，4 人（6％）に認められた．結語：実臨床において，C 型肝炎ウイルス遺伝子型 1 型慢性肝炎または代償性肝硬変患者に対するエルバスビルとグラゾプレビルの 12 週間治療は効果的で安全であった．