



Efficacy and Safety of Elbasvir/Grazoprevir Combination Therapy for Chronic Hepatitis C



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Abstract

Objective: A phase III clinical study of combination therapy with elbasvir (EBR) and grazoprevir (GZR) was conducted in Japan, and the additive therapeutic effects were obtained. In this study, we report safety and efficacy of EBR/GZR combination therapy in a real-world practice.

Methods: Sixty-two patients with chronic hepatitis C received EBR/GZR combination therapy from November 2016. Patients who achieved sustained virologic responses at 12 weeks (SVR12) were included in the study. A total of 40 patients were enrolled in this retrospective study. Thirty-eight patients were naive for direct-acting antiviral (DAA) therapy and two patients were previously treated with DAA.

Results: All of 38 DAA-naïve patients achieved SVR12 by EBR/GZR combination therapy, whereas two patients with DAA failure prior to this treatment did not achieve SVR12. A total of 21 patients (52.5%) had cardiovascular diseases, and 5 patients (12.5%) had advanced kidney diseases with eGFR<30. All of these patients achieved SVR12, and the treatment was performed safely even in the presence of cardiovascular and kidney diseases.

Conclusion: Clinical efficacy and safety of EBR/GZR combination therapy have been confirmed in this study. EBR/GZR combination therapy is extremely effective in chronic hepatitis C patients naive for DAA treatments. Administration of EBR and GZR therapy is safe in patients bearing cardiovascular and kidney disease.

Abbreviations: DAAs: Direct-acting antivirals; EBR: Elbasvir; GZR: Grazoprevir

Introduction

Eradication of hepatitis C virus is crucial for risk reduction of human hepatocarcinogenesis [1-3]. Direct-acting antiviral (DAA) agents such as telaprevir (TVR) [4-6] and simeprevir (SMV) [7-11] are the first ones that were introduced for the treatment of patients with chronic hepatitis C virus (HCV) infection from 2011 to 2013. Although these DAAs have improved the overall efficacy of chronic hepatitis C (CHC) treatment, TVR or SMV was used in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV). A significant population of patients with CHC were compelled to discontinue or skip scheduled treatments with triple therapy consisting of PEG-IFN, RBV, and TVR or SMV since this treatment regimen caused a wide variety of side effects such as anemia and liver dysfunction. Moreover, administration of PEG-IFN is accompanied by the appearance of high fever and general malaise, which sometimes impair the patients' quality of life. To overcome such disadvantages of triple therapy consisting of PEG-IFN, RBV, and TVR or SMV, combination therapy with asunaprevir

(ASV) and daclatasvir (DCV) was approved in 2014 as the first IFN-free regimen [12-15]. Compared with treatment regimens including IFN, this combination therapy can be applied to a broad range of patients.

Even the elderly patients with comorbidities have become good candidates for this IFN-free regimen. Different from IFN-based regimens, the efficacy of the combination therapy with ASV and DCV was not affected by patient characteristics, such as sex and age, or the presence of liver fibrosis and IL28B polymorphism. Although the combination therapy with ASV and DCV was safe with minimal adverse effects, the efficacy of this regimen was dependent upon the presence of baseline viral mutations that conferred resistance to the treatment. In addition, some patients were unable to continue the treatment due to side effects such as liver dysfunction. Combination therapy with sofosbuvir (SOF) and ledipasvir (LDV) is a second generation IFN-free regimen that can eliminate HCV bearing mutations resistant to ASV and DCV. A phase

III trial of combination therapy with SOF and LDV in Japan resulted in a remarkable success in the achievement of sustained viral responses (SVR) due to an additive effect of the two drugs [16]. Despite of extremely high elimination rates in CHC patients treated with SOF and LDV, two major concerns regarding this combination have been raised. Firstly, SOF is excreted by the kidneys and thus its use was contraindicated in patients with advanced kidney diseases. Secondly, combination therapy with SOF and LDV may have some toxic effects on cardiac functions leading to QT interval prolongation [17]. Combination therapy with elbasvir (EBR) and grazoprevir (GZR) is a third generation IFN-free regimen for CHC. A phase III trial of combination therapy with EBR and GZR has provided evidence that, this combination regimen is safe even in patients with advanced kidney diseases [18]. In the present study, we examined the efficacy and safety of EBR/GZR combination therapy in patients with CHC. Our results suggest that combination therapy with EBR and GZR is very effective even in elderly patients bearing impaired heart and kidney functions.

Patients and Methods

Patients and Treatment Schedule

Sixty-two patients with CHC received combination therapy with EBR and GZR at Kindai University Hospital from November 2016. Patients were included in this retrospective study if their sustained virologic responses at 12 weeks (SVR12) were able to be evaluated. A total of 40 patients were enrolled in the study. The combination therapy was administered for a total of 12 weeks, followed by 12 weeks observation. Patients received oral administration of 50 mg of EBR and 100 mg of GZR once daily for a total of 12 weeks. Ethical permission of this study was granted by the Review Boards of Kindai University Faculty of Medicine.

Quantification of HCV-RNA

HCV-RNA levels were measured using the Roche COBAS Taqman test with lower and upper limits of quantitation of 15 IU/mL and 8.0 log IU/mL.

HCV Mutation Analysis

HCV NS5A and NS3/4A mutations that confer drug resistance were examined using PCR-invader, CycleavePCR, and direct sequencing. Serum samples isolated from 13 patients were subjected to HCV mutation analysis.

Results

Patients

Sixty-two patients with CHC received combination therapy with EBR and GZR at our hospital from November 2016. Forty patients were included in the study, as their SVR12 were evaluable. As shown in Table 1 the median age of the patients was 74 years; 29 (73%) were over the age of 65 and 18 (45%) were over the age of 75. Thus, the number of elderly patients in our study was higher than that in the phase III clinical trial conducted in Japan [18]. In addition, 12 patients (30%) had cirrhosis and 7 (18%) had a previous history of liver cancer that was cured. There were 2 patients (5%) who had been previously treated with DAA; one patient was refractory to combination therapy with DCV and ASV,

whereas the other patient had experienced breakthrough with DCV and ASV and then relapsed with subsequent SOF and LDV (Table 1)

Baseline Resistance-Confering Mutations in NS5A

The presence of NS5A mutations was examined in 13 patients. NS5A mutations were not detected in six patients (15%), seven patients (18%) had Y93 mutations, and two patients (5%) had L31 mutations (Table 1).

Table 1: Patient background.

| Patient background | |
|------------------------------|-------------------------------------|
| Age, years | n=40 |
| Median (range) | 74 (19-86) |
| >65 years, n (%) | 29 (73%) |
| >75 years, n (%) | 18 (45%) |
| Male sex, n (%) | 18 (45%) |
| Cirrhosis, n (%) | 12 (30%) |
| History of HCC, n (%) | 7 (18%) |
| Previous DAAs therapy, n (%) | 2 (5%) DCV/ASV;1, DCV/ASV→SOF/LDV;1 |
| NS5A mutation | |
| Wild, n (%) | 6 (15%) |
| Y93, n (%) | 7 (18%) |
| L31, n (%) | 2 (5%) |
| N.E., n (%) | 27 (68%) |

Virologic Response

All 40 patients (100%) achieved end-of-treatment-response (ETR). Two patients had relapsed during the subsequent 12-week observation period. Thus, SVR12 was achieved in 38 patients (95%) (Figure 1).

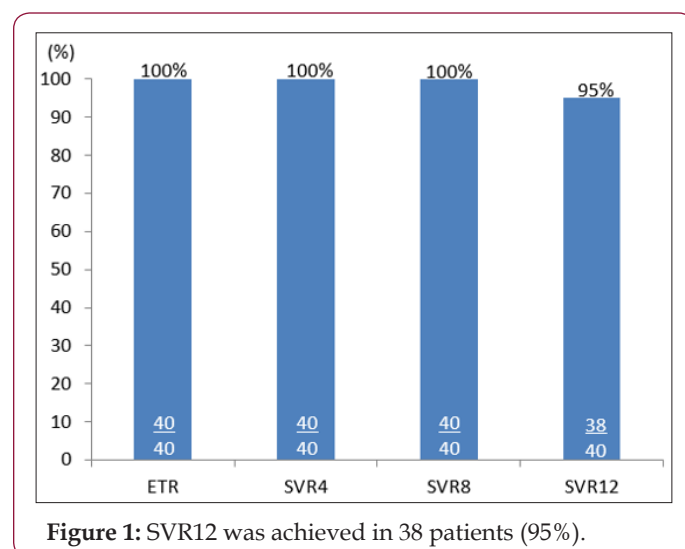


Figure 1: SVR12 was achieved in 38 patients (95%).

Virologic Relapse

Two patients who had previously been treated with DAA relapsed after the 12-week treatment. One of the patients was refractory to combination treatment with DCV and ASV and had acquired Y93H (100%) and L31M, V (>20%) mutations prior to the administration

of EBR and GZR. The other patient achieved breakthrough with DCV and ASV and then relapsed with subsequent combination treatment with SOF and LDV. This patient also had resistance mutations of Y93H (>20%) and L31M, V (>20%) prior to the administration of

Table 2: Characteristics of patients who did not achieve SVR.

| Age | Sex | Previous DAA therapy | Cirrhosis | History of HCC treatment | IL28B Rs 8099917 | Pre-treatment resistance | Side effects |
|-----|--------|--|-----------|--------------------------|------------------|---------------------------|--------------|
| 73 | Female | Refractory (DCV/ASV) | No | No | TT | Y93H (100%)L31M, V (>20%) | None |
| 79 | Female | BT (DCV/ASV) → Relapse (SOF/LDV) | No | No | TG | Y93H (>20%)L31V (>20%) | None |

Baseline NS5A (Y93) Resistance-Confering Mutation and Antiviral Efficacy of EBR and GZR Therapy in DAA-naïve patients

Five DAA-naïve patients had Y93H mutations in NS5A. Four

patients had a high frequency of resistance-confering mutations (≥50%). However, all patients achieved SVR12 (Table 3). Thus, the presence of baseline mutations in NS5A resistant to DAA did not affect the rates of SVR12 in DAA-naïve patients treated with EBR and GZR.

Table 3: Baseline resistance-confering mutations in NS5A in DAA-naïve patients.

| Age | Sex | Previous DAA therapy | L31 | Y93H | Cirrhosis | eGFR | SVR |
|-----|--------|----------------------|-----|--------------|-----------|------|-------|
| 77 | Male | None | (-) | Y93H (50%) | Yes | 7 | SVR12 |
| 82 | Female | None | (-) | Y93H (90%) | Yes | 58 | SVR12 |
| 70 | Male | None | (-) | Y93H (100%) | No | 5 | SVR12 |
| 42 | Male | None | (-) | Y93H (50%) | No | 61 | SVR12 |
| 78 | Female | None | (-) | Y93H (1-20%) | No | 65 | SVR12 |

Anti-viral Efficacy and Safety of EBR/GZR Therapy for Patients with Cardiovascular Disease

A total of 21 (52.5%) among the 40 patients had cardiovascular

diseases. All 21 patients achieved SVR12, and none had side effects, including heart disease (Figure 2). Thus, combination therapy with EBR and GZR is safe even patients with cardiovascular diseases.

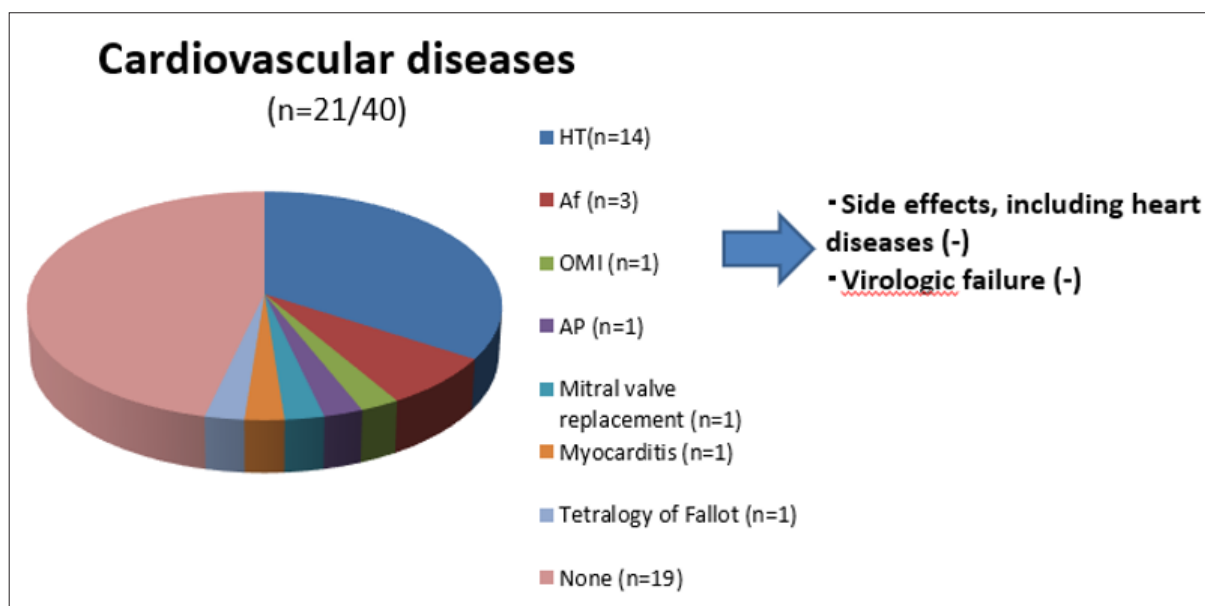


Figure 2: All 21 patients achieved SVR12, and none had side effects, including heart disease.

Anti-viral Efficacy and safety of EBR/GZR Therapy for Patients with Advanced kidney diseases (eGFR<30)

Table 4: Side effects leading to discontinuation of the therapy.

| N, (%) |
|-------------------------------|
| 1 (2.5%), increased ALT level |

Five of the 40 patients had advanced kidney diseases with eGFR<30. All 5 patients achieved SVR12, and none had side effects (Table 4). Thus, combination therapy with EBR and GZR is safe even

Table 5: Patients with advanced kidney diseases (eGFR<30).

| Age | Sex | Cirrhosis | Baseline mutation | SVR | HD | eGFR (pre) | eGFR (post) | Side effects |
|-----|------|-----------|-----------------------|-------|-----|------------|-------------|--------------|
| 79 | Male | No | N.E. | SVR12 | No | 21 | 20 | None |
| 77 | Male | Yes | Y93H (50%) L31(-) | SVR12 | Yes | 7 | 13 | None |
| 70 | Male | No | Y93H (100%) L31(-) | SVR12 | Yes | 5 | 6 | None |
| 55 | Male | No | N.E. | SVR12 | Yes | 6 | 4 | None |
| 74 | Male | Yes | N.E. | SVR12 | Yes | 8 | 9 | None |

Discussion

The Japanese phase III trial of combination treatment with EBR and GZR in DAA-naïve patients revealed that 96.5% of HCV-infected patients with liver cirrhosis and 97.1% of patients with compensated liver cirrhosis achieved SVR12 [18]. As for the presence of baseline NS5A mutations conferring resistance to DAA, the Japanese phase II and phase III trials disclosed that 93.1% of patients bearing such NS5A mutations achieved SVR12, suggesting that the presence of mutations do not affect the elimination rates of HCV in this combination therapy. [18]. In line with these trials, 38 of 40 patients (95%) achieved SVR12 in this study. The two patients who did not achieve SVR12 experienced treatment failure in prior DAA treatment. Moreover, they acquired mutations in Y93 and L31 prior to the initiation of EBR and GZR therapy. Thus, DAA-experienced patients who have already acquired resistance due to multiple mutations in NS5A may not be suitable candidates for EBR and GZR therapy. On the other hand, all of 38 DAA-naïve patients achieved SVR12 in this study. Although five of these patients had Y93H mutations and 4 had a high frequency ($\geq 50\%$) of resistance-conferring mutations, they all achieved SVR12. This suggests that the presence of resistance-conferring mutations does not influence the efficacy of EBR and GZR therapy in DAA-naïve patients. Although our study included a higher proportion of elderly patients and those with more advanced liver fibrosis as compared with the Japanese phase III trial, all of our patients achieved SVR. Therefore, combination therapy with EBR and GZR may be an effective treatment option for DAA-naïve patients with advanced liver cirrhosis. This study population consisted of a high proportion of patients with cardiovascular diseases.

It should be emphasized that combination therapy with EBR and GZR led to achievement of SVR 12 in all patients with cardiovascular diseases and none of such patients discontinued this treatment due to cardiovascular side effects. These data are in stark contrast

patients with advanced kidney diseases.

Side Effects leading to Discontinuation of EBR/GZR Therapy

Combination therapy with EBR and GZR was discontinued in one patient (2.5%) due to an increased level of alanine aminotransferase (ALT, 261 IU/mL) at week 10. The treatment was re-initiated after the reduction of ALT levels to complete the 12-week regimen (Table 5).

with those of previous studies regarding combination therapy with SOF and LDV in which such treatment may have some toxic effects on cardiac functions leading to QT interval prolongation [17]. Furthermore, several reports suggest that HCV infection and cirrhosis may cause QT interval prolongation and cardiovascular diseases such as angina [19-20]. Indeed, a significant population of patients who received combination therapy with SOF and LDV developed cardiovascular side effects, leading to discontinuation of the treatment. Our findings strongly suggest that combination therapy with EBR and GZR is safe and effective treatment option for patients with heart diseases. Both EBR and GZR are metabolized by CYP3A and can be administered safely to patients with kidney diseases. In phase II and phase III trials (C-SURFER), combination therapy with EBR and GZR treatment led to SVR12 in 99.1% of the patients with advanced stages of chronic kidney disease without serious adverse events [21].

In the present study, 5 of the 40 patients had advanced kidney diseases with eGFR<30, and all 5 patients achieved SVR12 without developing any side effects (Table 4). Thus, consistent with previous reports, this combination therapy was found to be a safe and effective treatment option for patients with advanced kidney diseases. These data altogether strongly support the idea that combination therapy with EBR and GZR is safe and effective even in elderly CHC patients with cardiovascular and kidney diseases. One patient (2.5%) developed side effects that led to discontinuation of the therapy due to the elevation of serum ALT levels. The patient skipped the treatment for 2 weeks and then was re-started after the confirmation of reduction of ALT levels to complete the 12-week regimen (Table 5). Clinical course of this patient suggest that close and careful monitoring of liver enzymes is might be required in combination therapy with EBR and GZR. In conclusion, we demonstrated that combination therapy with EBR and GZR is an effective treatment option for DAA-naïve patients bearing

advanced kidney diseases and cardiovascular diseases. Given the fact that an SVR rate of over 95% was achieved with DAAs further studies focusing on improvement of the safety are required. It is no doubt that combination therapy with EBR and GZR is one of such candidates that can be easily applied to the elderly CHC patients bearing a wide variety of comorbidities.

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