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Original Article

Efficacy and safety of elbasvir/grazoprevir treatment for Chinese patients with hepatitis C virus genotype 1b: a retrospective study

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Abstract: Objectives: To determine the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) treatment in Chinese patients with GT1b chronic hepatitis virus C (HCV) infections. Methods: In this retrospective study, 49 treatment-naive patients with chronic GT1b HCV infection were treated with GZR (100 mg) plus EBR (50 mg) for 12 weeks. The viral response was the primary endpoint and fibrosis stage changes during and after treatment, as well as the incidence of treatment-emergent adverse events (TEAE) were secondary endpoints. Results: After 2-week EBR/GZR treatment, the virologic response rate was 85.1% (80/94) and reached 100% (94/94) after 8 and 12 weeks of therapy. Sustained virologic response (SVR) rates were 100% at the 12, 24 and 48-week follow-ups. Multivariate analysis revealed that the baseline viral load of HCV RNA may affect the rapid 2-week virologic response (OR: 0.36, 95% CI: 0.14-0.92, P=0.034), but did not influence efficacy during further treatment or follow-ups. Fifteen patients with ≥1 TEAE (16.0%) were observed and 7 (7.4%) and 8 (8.5%) patients had mild ALT or AST elevations (1.1-2.5× BL), but no serious drug-related AEs occurred. Liver stiffness measurement (LSM), the AST to platelet ratio index (APRI) and the fibrosis index based on 4 factor (FIB4) scores were consistently reduced, especially in patients with high baseline assessments after 12 weeks' treatment and during follow-ups. Conclusions: A 12-week EBR/GZR regimen shows high efficacy and safety in Chinese patients with GT1b HCV infections.

Keywords: Hepatitis C, liver cirrhosis, elbasvir, grazoprevir, liver fibrosis

Introduction

Hepatitis C virus (HCV) is one of the causes for hepatocellular carcinoma (HCC), liver cirrhosis and many deaths due to liver failure, and it is also necessary for some patients to have a life-saving liver transplant [1, 2]. Recent epidemiological studies have revealed that 71.1 million people worldwide suffer from chronic HCV infections [3] and the World Health Organization estimated a death rate in 2016 of 350,000–500,000 people annually caused by HCV related liver diseases such as liver cirrhosis or HCC [4]. These major effects on the mortality and morbidity of affected individuals have attracted increased international attention [5, 6], not least because they place heavy healthcare and economic burdens on countries globally [7-9].

At least 7 HCV genotypes (GT) have been classified [10], with major regional differences in the worldwide distribution and rate of occurrence of each genotype. Among them, genotype 1 has the highest prevalence globally (44-46%). In China, approximately 10 million people have chronic HCV infections, making it one of the countries with the most HCV carriers [11]. The dominant genotype is GT1b, which accounts for >56.8% of all HCV infections while GT1a (1.4%) and G4 (0.2%) are rarely seen in clinical practice [12, 13].

Providing antiviral medication for HCV infection significantly lowers all-cause mortality, even in liver cirrhosis patients [14, 15]. A revolution in HCV treatment occurred when interferon-free, direct-acting antiviral (DAA) therapy was introduced into clinical practice, which exhibited exceptional efficacy and safety profiles compared to interferon (IFN) therapy. All HCV-infected individuals are strongly recommended to be given treatment, except those with a lim-

ited life expectancy. Elbasvir/grazoprevir (EBR/GZR) is a highly potent treatment regimen containing the nonstructural protein (NS) 3/4A inhibitor GZR and EBR, a NS5A inhibitor that has recently been introduced into clinical practice to treat chronic HCV genotypes 1 and 4 infections. Several phase 3 randomized clinical trials have demonstrated that EBR/GZR has an excellent therapeutic effect on patients suffering from chronic hepatitis C infections, regardless of whether they have concomitant chronic kidney disease (CKD), a HIV co-infection or other comorbidities [16-18]. Zepatier® (EBR/GZR) was approved for use in China in May, 2018, and to date EBR/GZR remains the recommended first-line treatment option in published Chinese and worldwide HCV guidelines [19-21]. EBR/GZR was launched in China nearly 2 years ago, but it seems that there was a lack of consolidated domestic data to reinforce its efficacy and safety profile, especially in Chinese patients. There is no doubt that DAA treatment has a positive impact in long-term follow-ups such as fibrosis stage reversion, which has been confirmed in western populations [22, 23]. The local data in Chinese patients remains to be unequivocally established, and this retrospective study was therefore conducted to establish definitive real-world studies on EBR/GZR utilization in Chinese patients.

Materials and methods

Patients

Information was retrospectively collected from 94 chronic hepatitis C (CHC) patients with or without compensated cirrhosis who were treated with EBR/GZR in the Lanzhou University Second Hospital between August 1, 2018 and October 31, 2019. The ethics committee of the Lanzhou University Second Hospital approved the protocol (approval number 2020A-169), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients who participated in the study. All recruited patients were treatment-naïve with a GT1b infection and had HCV RNA serum levels of ≥15 IU/mL.

Inclusion criteria: (1) Patients with an age ≥18 years old; (2) Patients with HCV GT1b infection; (3) Patients with serum HCV RNA level ≥15 IU/mL (COBAS TaqMan); and (4) Patients with compensated cirrhosis with Child Pugh Grade A.

Exclusion criteria: (1) Non-HCV GT1b patients; (2) Treatment-experienced HCV GT1b patients; (3) Treatment-naive HCV GT1b patients with decompensated cirrhosis with Child Pugh Grade B or C; (4) Treatment-naive HCV GT1b patients with unavoidable drug-drug interactions (DDI) during the treatment of complications; and (5) Treatment-naive HCV GT1b patients with cancer.

All patients received the DAA regime which was comprised of 50 mg EBR +100 mg GZR for 12 weeks, orally administered once a day. After cessation of treatment, follow-ups were conducted for 48 weeks. Routine blood tests were conducted and aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and total bilirubin concentrations were the indicators used to assess the viability of liver functions.

HCV RNA quantification was tested using a commercial kit (COBAS AmpliPrep/COBAS TaqMan viral load detection system; ver. 2.0, Roche Molecular Diagnostics, US) to detect plasma HCV RNA levels, with the lowest measurable quantitation limit being 15 IU/mL. HCV-GT measurements were made using a Real Time HCV Genotype II assay (Abbott Molecular Inc., US). Liver stiffness measurements (LSM) were carried out on all patients using FibroScan® (Echosens, France). A total of 10 measurements were made on each patient and the median liver stiffness calculated in units of kPa. This approach was based on the method described in previous studies [24]. The cut-off values for FibroScan (kPa) were <7.3, ≥7.3, ≥9.3 and ≥14.6 [25].

The AST to platelet ratio index (APRI) and fibrosis index based on 4 factors (FIB4) scores were calculated as: APRI = [{AST (international unit/L)/AST upper limit of normal (international unit/L)} ×100]/platelet count (10^9/L); FIB4 = age (years) × AST (international unit/L)/platelet count (10^9/L) × [ALT (international unit/L)$^{1/2}$]. APRI and FIB4 scores as negative predictive and positive predictive values of liver fibrosis were suggested to be 0.5 and 1 for APRI as well as 1.45 and 3.25 for FIB4 [26].

Outcomes

Primary endpoints: Treatment efficacy was assessed with a sustained virologic response (SVR), defined as undetectable HCV RNA at 12,

Table 1. Baseline characteristics of the 94 patients infected with HCV-GT1b

Variable	Patients (N=94)
Epidemiological characteristics	
Gender	
Male, n (%)	48 (51.1)
Female, n (%)	46 (48.9)
Age, mean ± SD (years)	47.32±13.77
HCV infection parameters	
HCV RNA (log IU/mL)	6.09±0.76
LVL (HCV-RNA ≤800,000 IU/mL), n (%)	31 (33.0)
HVL (HCV-RNA >800,000 IU/mL), n (%)	63 (67.0)
Elastography, APRI and FIB4 scores, n (%)	
LSM	
<7.3 kPa	57 (60.6)
≥7.3 kPa, <9.3 kPa	10 (10.6)
≥9.3 kPa, <14.6 kPa	13 (13.8)
≥14.6 kPa	14 (14.9)
APRI	
<0.5	11 (11.7)
≥0.5, <1.0	37 (39.4)
≥1.0	46 (48.9)
FIB4	
<1.45	34 (36.2)
≥1.45, <3.25	42 (44.7)
≥3.25	18 (19.1)
Laboratory parameters	
ALT (U/L), mean ± SD	68.53±48.50
AST (U/L), mean ± SD	57.85±32.97
TBIL (μmol/L), mean ± SD	19.17±9.35
WBC (10^9/L), mean ± SD	5.30±1.41
Hb (g/L), mean ± SD	149.31±23.12
PLT (10^{12}/L), mean ± SD	170.33±58.24
LSM (kPa), mean ± SD	9.46±7.03

Note: ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB4, fibrosis index based on four factors; Hb, hemoglobin; HCV, hepatitis C virus; LSM, liver stiffness measurement; LSM, liver stiffness measurement; PLT, blood platelets; TBIL, total bilirubin; WBC, white blood cells; SD, standard deviation.

24 and 48 weeks after completion of treatment.

Secondary endpoints: (1) On-treatment virologic response at the 2nd and 8th week and at cessation of the treatment, and the risk factors affecting the viral response during early treatment. (2) The incidence of AEs during EBR/GZR treatment. (3) Changes in liver function (ALT/AST/TBIL) during EBR/GZR therapy and at the 24th week and 48th week of follow-up, and (4) LSM, APRI and FIB4 scores at baseline after 12 weeks' EBR/GZR treatment, and at the 12th, 24th and 48th week of follow-up.

Statistical analysis

SPSS ver. 19.0 software for Windows (IBM SPSS Statistics, Chicago, IL, US) was employed for all data analysis. Normally distributed variables are expressed as the mean ± standard deviation and categorical data as percentages. Chi-squared and Wilcoxon rank sum tests were carried out to compare categorical data and continuous variables between the 2 groups, respectively. Risk factors affecting the virologic response rate after 2-week EBR/GZR therapy were evaluated using univariate and multivariate logistic regression analysis. A receiver operating characteristic (ROC) curve was used to identify the cut-off values of the HCV RNA titer associated with rapid virologic responses (RVRs). Correlations between LSM, APRI and FIB4 scores were determined using Pearson's correlation and a mixed effect model analysis of APRI, LSM and FIB4 with APRI as the dependent variable revealed correlations between treatment and follow-up changes of the indicators. A *P*-value <0.05 was considered to be a significant finding.

Results

Baseline and demographics of enrolled patients

Of the 94 patients enrolled, 48 were male (51.1%) with an age range of 23-76 years old (mean 47.32 years). The average HCV RNA value was 6.09±0.76 log IU/mL. According to a Pearson's correlation determination, baseline values of the LSM values, APRI and FIB4 correlated significantly with each other (see Table S1). Baseline results of laboratory analyses including routine blood and liver function tests are presented in **Table 1**. High viral load (HVL) has been preset as HCV RNA values of >400,000 IU/mL to >800,000 IU/mL [27, 28].

Primary endpoint

Virologic response rate: All 94 patients completed the 12-week EBR/GZR treatment regi-

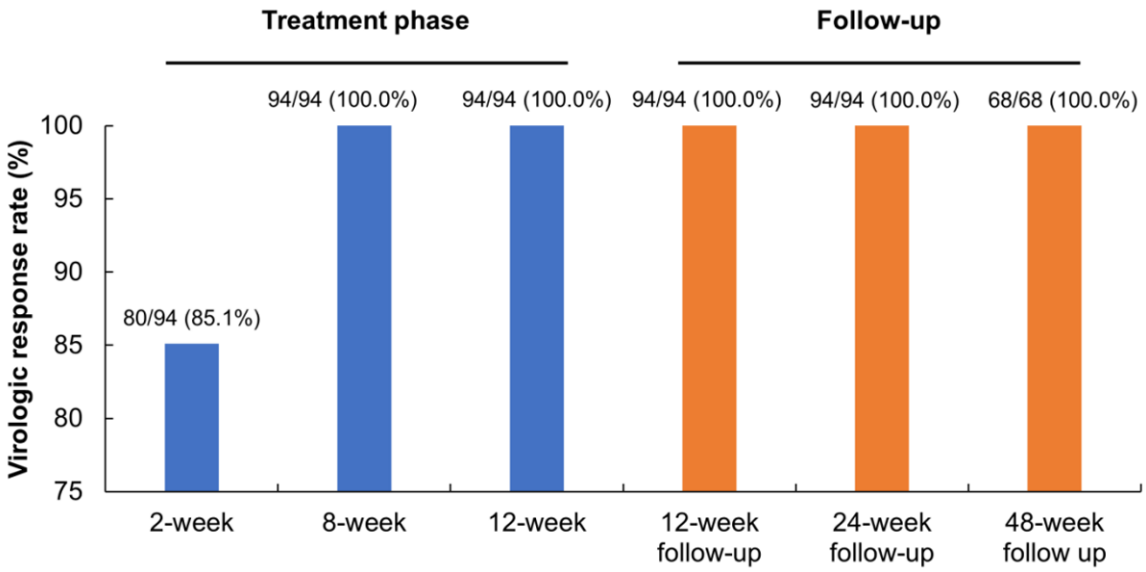

Figure 1. Virologic response to EBR/GZR during the treatment phase and follow-up. Note: EBR, elbasvir; GZR, grazoprevir; SVR, sustained virologic response.

men and the 12-week and 24-week follow-ups, while 68 patients finished the 48-week follow-up. After 2 weeks' EBR/GZR treatment, the virologic response rate was 85.1% (80/94) and reached 100% (94/94) at 8th week and after cessation of therapy (12 weeks). After treatments, all SVR rates were 100% during the follow up periods (12-weeks, 24-weeks and 48-weeks) (**Figure 1**).

Secondary endpoints

Risk factors affecting the virologic response after 2 weeks treatment: After 2-weeks EBR/GZR treatment, the virologic response rate was 85.1% (80/94) and reached 100% (94/94) at 8th week and after cessation of therapy. Therefore, the factors that may have affected the RVR were analyzed. After univariate analysis, HCV RNA, AST and hemoglobin (Hb) were found to be the factors that affected the virologic response at the 2nd treatment week. Previously published high HCV RNA levels up to 800,000 IU/mL did not have significant associations with the virologic response at 2nd week, but a ROC curve analysis revealed a HCV RNA threshold value of 3,290,000 IU/mL (sensitivity 76.2%, specificity 57.1%, Figure S1) for a high vs. low HCV RNA titer, which was significantly associated with the RVR (P=0.016). Also, after correction by multiple regression analysis, HCV RNA was proven to be the only risk factor that was directly associated with failure of the RVR (OR: 0.36, 95% CI: 0.14-0.92, P=0.034) (**Table 2**).

Adverse events (AEs) that occurred during EBR/GZR therapy: The percentage of patients who exhibited more than 1 treatment-emergent AE (TEAE) was 16.0% (15/94). Among them, there were 7 cases (7.4%) of elevated ALT (1.1-2.5× BL), 8 cases (8.5%) of elevated AST (1.1-2.5× BL), 4 cases (4.3%) of fatigue, 1 case (1.1%) of dizziness and 1 case (1.1%) of arthralgia. However, no serious adverse events (SAEs) were reported that were a threat to life, or lead to discontinuation of treatment or resulted in death (**Table 3**). For patients with elevations in ALT or AST, only 1 was cirrhotic (LSM ≥14.6) in each subgroup. For all patients who completed 24-week follow-ups, AST and ALT values were restored to normal.

Changes in liver functions (ALT/AST/TBIL) during EBR/GZR therapy and at 24th week and 48th week of follow-up: Changes, especially in ALT and AST concentrations during treatment and at follow-up revealed that liver functions most obviously improved after early treatment and were restored to normal, particularly in LSM patients with LSM values <9.3 kPa after eradication of the virus (**Figure 2**).

Changes of LSM, APRI and FIB4 values during EBR/GZR therapy and at 24th week and 48th week of follow-up: The value reductions in patients with baseline LSM <7.3 kPa (P=0.003), 7.3≤ LSM <9.3 kPa (P=0.001), 9.3≤ LSM <14.6 kPa (P<0.001) and LSM ≥14.6 kPa (P<0.001)

Table 2. Univariate analysis and multivariate analysis of the baseline factors linked to failure of the virologic response after 2-week treatment with EBR/GZR

	Virologic response at week 2		*P*-value	OR (95% CI)
	No-response (N=14)	Response (N=80)		
Univariate analysis				
Gender (Male/Female)				
Male	9 (64.3)	39 (48.7)		1.0
Female	5 (35.7)	41 (51.3)	0.289	1.89 (0.58-6.15)
Age (years)	46.14±11.99	47.53±14.11	0.728	1.01 (0.97-1.05)
HCV RNA (log IU/mL)	6.50±0.65	6.02±0.76	0.034	0.36 (0.14-0.92)
HCV RNA (IU/mL)				
LVL 1 (≤400,000 IU/mL)	1 (7.1)	19 (23.7)		1.0
HVL 1 (>400,000 IU/mL)	13 (92.9)	61 (76.3)	0.288	0.25 (0.03-2.01)
LVL 2 (≤600,000 IU/mL)	2 (14.3)	23 (28.7)		1.0
HVL 2 (>600,000 IU/mL)	12 (85.7)	57 (71.3)	0.340	0.41 (0.09-1.99)
LVL 3 (≤800,000 IU/mL)	2 (14.3)	29 (36.3)		1.0
HVL 3 (>800,000 IU/mL)	12 (85.7)	51 (63.7)	0.124	0.29 (0.06-1.40)
LVL 4 (≤3,290,000 IU/mL)	6 (42.9)	61 (76.3)		1.0
HVL 4 (>3,290,000 IU/mL)	8 (57.1)	19 (23.7)	0.016	0.23 (0.07-0.76)
Elastography, APRI and FIB4 scores, n (%)				
LSM				
LSM <7.3 kPa	7 (50.0)	50 (62.5)		1.0
7.3 kPa ≤ LSM <9.3 kPa	1 (7.1)	9 (11.3)	0.838	1.26 (0.14-11.51)
9.3 kPa ≤ LSM <14.6 kPa	4 (28.6)	9 (11.3)	0.111	0.32 (0.08-1.30)
LSM ≥14.6 kPa	2 (14.3)	12 (15.0)	0.840	0.84 (0.16-4.57)
APRI				
<0.5	0 (0.0)	11 (13.8)	0.969	----
≥0.5, <1.0	4 (28.6)	33 (41.3)	0.194	2.29 (0.66-8.02)
≥1.0	10 (71.4)	36 (45.0)		1.0
FIB4				
<1.45	3 (21.4)	31 (38.8)		1.0
≥1.45, <3.25	7 (50.0)	35 (43.8)	0.322	0.48 (0.12-2.04)
≥3.25	4 (28.6)	14 (17.5)	0.192	0.34 (0.07-1.72)
Laboratory parameters, mean ± SD				
ALT (U/L)	88.83±49.18	64.98±47.8	0.103	0.99 (0.98-1.00)
AST (U/L)	74.04±34.01	55.02±32.17	0.054	0.99 (0.97-1.00)
TBIL (μmol/L)	20.59±5.13	18.93±9.90	0.543	0.98 (0.93-1.04)
WBC	5.57±1.40	5.26±1.42	0.440	0.86 (0.59-1.26)
Hb (g/L)	161.00±16.21	147.26±23.61	0.043	0.97 (0.94-0.99)
PLT (10^9/L)	152.00±59.58	173.54±57.79	0.204	1.01 (1.00-1.02)
LSM	12.26±10.21	8.97±6.27	0.119	0.95 (0.89-1.01)
Multivariate analysis				
HCV RNA (log IU/mL)			0.034	0.36 (0.14-0.92)

Note: ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB4, fibrosis index based on four factors; Hb, hemoglobin; HCV, hepatitis C virus; HVL, high virus load; LSM, liver stiffness measurement; LVL, low virus load; PLT, blood platelets; TBIL, total bilirubin; WBC, white blood cells; SD, standard deviation.

as well as 0.5≤ APRI <1 (P<0.001), APRI ≥1 (P<0.001) and 1.45≤ FIB4 <3.25 (P<0.001) and FIB4 ≥3.25 (P<0.001) during treatment and the follow-up levels were constantly improved. Compared to baseline levels, patients with basic APRI <0.5 did not exhibit significant

Table 3. Adverse events that occurred in patients with HCV-GT1b during the 12-week treatment

Adverse events	N=94 (%)
At least 1 TEAE	15 (16.0)
Fatigue	4 (4.3)
Dizziness	1 (1.1)
Arthralgia	1 (1.1)
SAE	0 (0.0)
Life-threatening SAE	0 (0.0)
Discontinuation due to AEs	0 (0.0)
SAE leading to death	0 (0.0)
Laboratory test abnormal	
ALT elevation (1.1-2.5× BL)	7 (7.4)
ALT elevation (2.5-5× BL)	0 (0.0)
AST elevation (1.1-2.5× BL)	8 (8.5)
AST elevation (2.5-5× BL)	0 (0.0)
TBIL elevation (2.5-5× BL)	0 (0.0)
TBIL elevation (>5× BL)	0 (0.0)

Note: HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TBIL, total bilirubin; TEAE, treatment emergent adverse event.

changes in their APRI scores at 12th week treatment (P=0.210) and 24th week follow-ups (P=0.638), but the APRI scores significantly increased at the 48th week follow-up (P=0.001). FIB4 <1.45 scores did not significantly change during treatments or at follow-up compared to their base line values (all P>0.05) (**Figure 3**). A mixed effect model analysis of APRI, LSM and FIB4 with APRI as the dependent variable revealed significant correlations between treatment and follow-up changes of the indicators (Table S2).

Discussion

The present study is one of the few observational investigations into the safety and efficacy of EBR/GZR therapy in Chinese treatment-naïve patients infected with HCV-GT1b. First, we investigated the effectiveness of EBR/GZR therapy and found after 12 weeks' treatment, SVR12 occurred in 100% (94/94) of treated patients. The results confirmed that a period of 12-week treatment was very effective for Chinese GT1b patients, which were comparable to published data from phase 2/3 clinical trials [29-38] and other real-world studies [39-44]. For many reasons (fairly effective for the PR regime, utilization of illegal DAAs, etc.), patients who experienced PR treatment are not very common in Chinese clinical practice and GT1a/4 has a low prevalence in the Chinese population. These patients were not recruited into the study, and we could not draw any definitive conclusion about them. Furthermore, with great consistency, no difference in SVR12 and SVR24 was observed regardless of patient age, gender, baseline HCV RNA levels and LSM, or APRI and FIB4 scores in the GT1b cohort. It has been reported, that baseline viral load may affect the Peg-IFN/ribavirin treatment outcomes of HCV genotype 1 patients [45]. HVL is very common in Chinese practice (67% in this study), and we determined the viral kinetics during treatment and the relationship between RVR and SVR. When determining HVL ≥800.000 IU/mL, there was no correlation between HVL and SVR. However, the present study revealed that a significant correlation between high HCV RNA baseline virus load and 2-week RVR outcomes for EBR/GZR treatment still existed, but the threshold was 3,290.000 IU/mL and did not affect the virologic response rates by treatment weeks of 8 and 12, nor SVR rates at the follow-ups weeks of 12, 24 and 48.

We also evaluated the safety profile of the study population. The safety data obtained from a Chinese GT1b population who received EBR/GZR therapy for 12 weeks were similar to previously published reports for both Western and Asian patients [46]. The AEs reported in this study were also the same AEs mentioned in the drug instruction leaflet, while patients had been informed of the safety issues of Zepatier® before taking the drug. This might explain why the TEAE rate was different from that reported in the C-CORAL study [47] and might also reflect the difference between real world and phase 3 double-blind studies.

The most frequent TEAE was fatigue, which was observed in 4 patients (4.3%). All the AEs detected during therapy were clinically acceptable and none were severe. No patient experienced an SAE or discontinued therapy for any reason. Since EBR/GZR is a PI containing regime that has the potential risk to cause liver toxicity, treatment emergent liver injury is a major concern when administering EBR/GZR therapy. Only 7.4% (7/94) and 8.5% (8/94) of

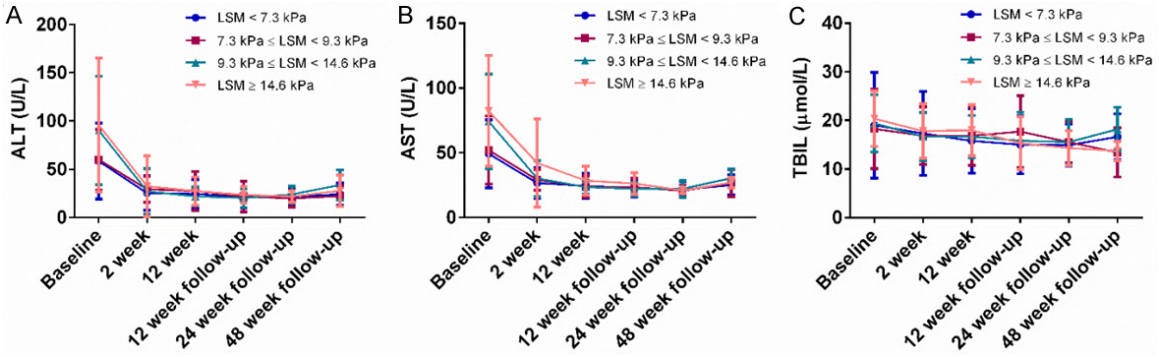

Figure 2. Liver enzyme determinations during and after EBR/GZR therapy. (A) ALT, (B) AST and (C) TBIL concentrations at time points in patients with indicated baseline LSM values. Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBR, elbasvir; GZR, grazoprevir; TBIL, total bilirubin.

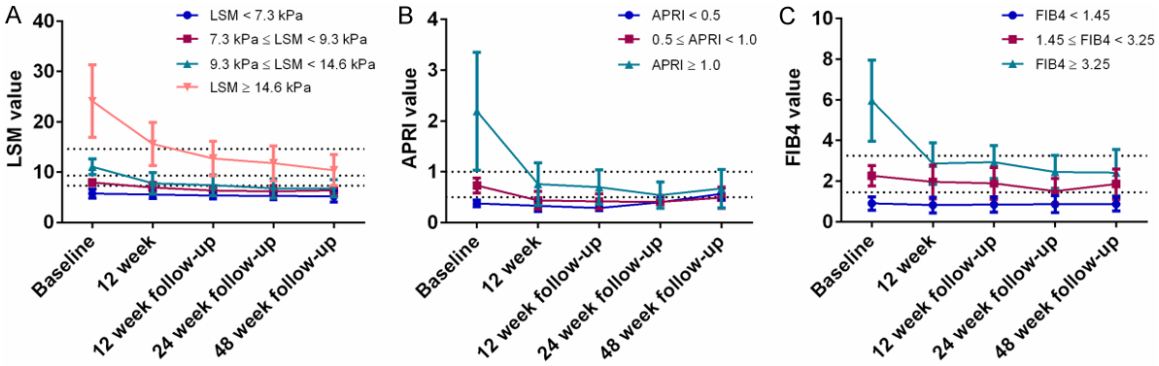

Figure 3. LSM, APRI and FIB4 determinations during and after EBR/GZR therapy. (A) LSM, (B) APRI and (C) FIB4 changes in patients with indicated baseline values during and after EBR/GZR therapy. Dotted lines indicate the borders of the different score groups. Note: APRI, aspartate aminotransferase to platelet ratio index; EBR, elbasvir; FIB4, fibrosis index based on four factors; GZR, grazoprevir; LSM, liver stiffness measurement.

patients with mild ALT or AST elevation (1.1-2.5× BL) were identified. Of particular interest was the finding that cirrhosis was not a risk factor for ALT/AST elevation. Treatment emergent ALT/AST elevation was improved and restored to normal after cessation of treatment. No patients experienced ALT/AST >2.5× BL or TBIL >2.5× BL. All of our findings suggested that EBR/GZR can be safely administered to patients, even to those with compensatory cirrhosis. It should be noted that EBR/GZR is contraindicated in individuals suffering from decompensated cirrhosis (Child-Pugh B or C) [48, 49], because of significantly increased exposure to grazoprevir [46].

Disease development of an HCV infection is characterized by liver fibrosis, which progresses from minimal histological impairment to extensive and advanced fibrosis [50]. Previous research proposed LSM values as indicators for liver fibrosis [24], with cut-off values for FibroScan of >9.5 kPa for determining advanced fibrosis [51]. However, there is a discrepancy of opinion whether LSM values truly reflect fibrosis, as the published threshold values vary between different research groups [52-54]. In addition to TE, other noninvasive tests for liver fibrosis have been introduced, of which APRI and FIB4 are the most commonly employed [55]. The results of the present study showed that the magnitudes of LSM, APRI and FIB4 scores consistently improved compared with baseline after treatment, which is in accordance with previous research and reflects agreement with other studies showing resolution of chronic liver inflammation and improvement of necroinflammation [56-58]. However, reductions of the scores were most obvious in patients with the initial highest scores, which is in line with a previous study on HCV treatments with DAA medication [59].

Our study had a number of limitations. First, it was retrospective in nature and the attending physician selected the candidate patients who were to receive EBR/GZR therapy. Second, it was a single-center study with a limited cohort of patients. Third, the promising reversal of LSM, APRI and FIB4 in HCV patients after EBR/GZR therapy should be further evaluated in a multi-center large cohort study involving long-term follow-ups.

Conclusions

A 12-week course of EBR/GZR therapy is effective in treating patients with HCV-1b infections, and disease progression can be partially reversed.

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Disclosure of conflict of interest

None.

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Table S1. Pearson's correlations among the parameters analyzed in the study at baseline

Parameters	FIB4	APRI	LSM
FIB4	r=1.000	r=0.777, P<0.001	r=0.505, P<0.001
APRI	/	r=1.000	r=0.548, P<0.001
LSM	/	/	r=1.000

Note: APRI, aspartate aminotransferase to platelet ratio index; FIB4, fibrosis index based on 4 factors; LSM, liver stiffness measurement.

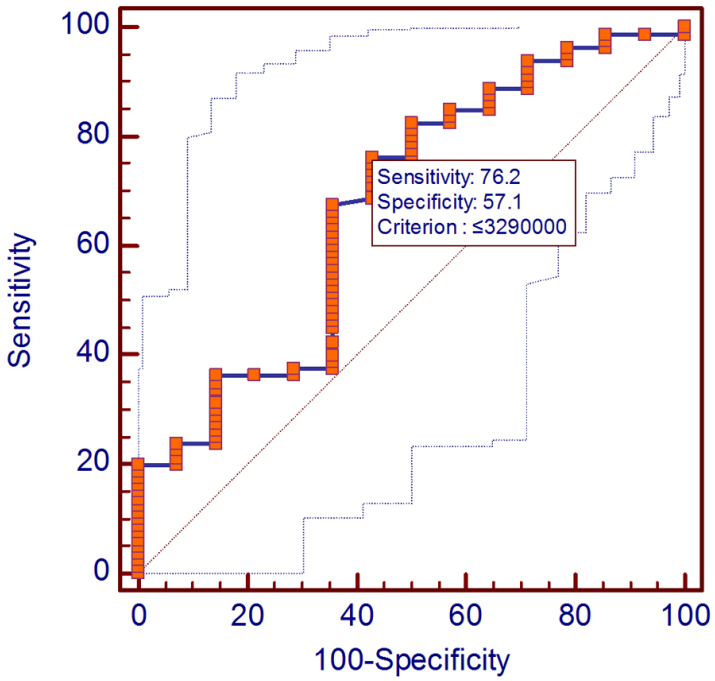

Figure S1. ROC curve for the results of the HCV-RNA level associated with early virologic response. The criteria for the cut-off value were the highest sensitivity and specificity (greatest proximity to the upper left corner of the graph).

Table S2. Mixed effect model analysis of APRI, LSM and FIB4 with APRI as the dependent variable

	Estimates	SD	*P*-value
FIB4	0.349	0.021	<0.001
LSM	0.029	0.007	<0.001

Note: APRI, aspartate aminotransferase to platelet ratio index; FIB4, fibrosis index based on four factors; LSM, liver stiffness measurement.