Effectiveness of Elbasvir and Grazoprevir Combination and 1-year Follow-up Hepatic Function for HCV Genotype 1b Infection: Results From a Chinese Real-world Cohort.

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Research

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Abstract

Background: The treatment of chronic hepatitis C (CHC) has entered the interferon-free era since the approval of all-oral direct-acting antiviral (DAA) therapy in China. Twelve weeks of Elbasvir and Grazoprevir (EBR/GZR) has been demonstrated to be highly effective and well tolerated in phase III registration trials in Asia. However, real-world data on this regimen are lacking in mainland China. We aimed to evaluate the efficacy and safety of EBR/GZR and hepatic function during 1-year follow-up in real-world clinical practice with genotype 1b HCV infection.

Methods: A prospective, multicenter, non-interventional cohort study was conducted in Tianjin Third Central Hospital and Tianjin Second People's Hospital of China. All patients diagnosed with HCV-1b infection and treated with EBR/GZR for 12 weeks were included. The sustained virological response (SVR) rate obtained 12 weeks posttreatment (SVR12) and week 48 posttreatment (SVR48), the liver function and safety were also evaluated in patients who received EBR/GZR.

Results: A total of 251 patients were enrolled, 215 of whom completed the 12-week treatment and 107 completed the 48-week follow-up after treatment. 47 patients (21.9%) had compensatory cirrhosis. The overall rates at the end of treatment (EOT), SVR12 and SVR48 were 100%, 99.5% and 99.1%, respectively. Two cirrhosis patients relapsed at 12 weeks and 48 weeks posttreatment respectively. At 48 weeks posttreatment, the normalization rate of ALT and AST were increased significantly than that of baseline (97.2% and 95.3% vs 59.5% and 61.4%, $P<0.01$). The incidence of any adverse reactions was 18.1%, while most reactions were mild in severity.

Conclusion: In a real-world cohort, treatment with EBR/GZR in Chinese patients with genotype 1b HCV infection appears to be well tolerated and achieves high SVR12 and SVR48 rates.

Trial registration: ChiCTR, ChiCTR1900023747. Registered 10 June 2019, Retrospectively registered. http://www.chictr.org.cn/showproj.aspx?proj=39926

Introduction

Chronic hepatitis C (CHC) is a chronic, progressive disease that occurs worldwide and greatly threatens human health[1, 2]. In China, hepatitis C virus infection is one of the most important causes of cirrhosis and hepatocellular carcinoma[3]. Because of the excellent efficacy and limited course of direct-acting antiviral drugs (DAA), interferon-free oral antiviral drugs have been recommended as first-line antiviral therapy for chronic hepatitis C patients[4]. With the introduction of direct-acting antiviral drugs in China, hepatitis C treatment has progressed from interferon to the DAA era.

Genotype 1b HCV accounts for 62.7% of HCV infections in China[5]. Combination therapy with Elbasvir (EBR) /Grazoprevir (GZR) has been demonstrated to be safe and highly effective for genotype-1 hepatitis C virus (HCV)-infected patients in phase III registration trials in Asia[6] and approved for use in Chinese patients with hepatitis C since November 2018. However, the real-world data regarding this regimen in

Chinese patients are not well known. We aimed to evaluate the efficacy and safety of Elbasvir/Grazoprevir for the treatment of Chinese patients with chronic HCV genotype 1b infection in the 1-year follow-up.

Patients And Methods

Study population

In this prospective, multicenter, noninterventional cohort study, patients with genotype 1b chronic hepatitis C and compensated cirrhosis who received a 12-week treatment course with EBR /GZR from November 1, 2018, to August 31, 2019, in Tianjin Third Central Hospital and Tianjin 2nd People's Hospital were continuously enrolled.

Adult patients (> 18 years old) diagnosed with chronic HCV-1 infection and treated with EBR /GZR were eligible for this study. Chronic hepatitis C virus infection, defined as detectable hepatitis C virus antibodies and quantifiable serum HCV RNA by using the COBAS TaqMan HCV Kit (Roche Diagnosis Co, Ltd, Mannheim, Germany, detection limit [LLOD]: 15 IU/ml), lasted for more than six months. The diagnosis of liver cirrhosis was based on transient elastography exceeding 12.5 kPa[7] and a liver imaging examination (ultrasonography, computed tomography or MR imaging) that revealed signs of cirrhosis (e.g., atrophy of the right lobe of the liver, irregularity of the hepatic surface, and splenomegaly) in combination with the clinical state. The exclusion criteria were as follows: decompensated cirrhosis, coinfection with HBV or HIV, self-withdrawal during treatment due to non-drug reasons, treatment duration less or more than 12 weeks, incomplete data, loss to follow-up or previous history of DAA drug use.

Patients enrolled in the study received EBR (100 mg) and GZR (50 mg) once daily without ribavirin for 12 weeks. The clinical, laboratory and virological parameters were assessed at baseline, end of treatment, 12 weeks and 48 weeks after treatment completion. HCV RNA was detected using a Roche COBAS HCV Kit with a range of 15 ~ $6.9*10^7$ IU/ml. This observational study was approved by the Ethics Committee of Tianjin Third Central Hospital and Tianjin 2nd People's Hospital. Informed consent was obtained from all the patients prior to study initiation.

Evaluations of efficacy and safety

Virologic response, defined as undetectable HCV RNA, was assessed at the end of treatment (EOT), at week 12 (SVR12) posttreatment and week 48 (SVR 48) posttreatment. Improvements in liver function were also assessed at the same time.

Any adverse events (AEs), including clinical and biochemical abnormalities associated with treatment reported by patients during treatment, were recorded. The MedDRA system is used to code adverse events and associated diseases[8]. Details of all recorded serious adverse events (SAEs) were collected by the treating physicians. SAEs were defined as any life-threatening event, an event that led to hospital admission, or one that resulted in death.

Statistics

All the statistical analyses were performed using SPSS software, version 22.0 (IBM Corporation, Somers, NY, USA). Quantitative variables are presented as and range when appropriate. The viral responses are shown in numbers and percentages with 95% confidence intervals (CIs). A two-sided p-value of < 0.05 was considered statistically significant. The statistical analysis was performed.

Results

Baseline Characteristics of Patients

From November 1, 2018, to August 31, 2019, 468 HCV-1 infection patients were enrolled in this observational cohort study in the two medical centers. A total of 215 patients met the admission criteria and completed the course of treatment and 12-week' follow-up,107 patients completed 48-week' follow-up by the end of Nov 2020, shown in Fig. 1. Of these 215 patients with an average age of 60 years, 8 patients had previously been treated with interferon and ribavirin before DAA treatment. Among the baseline population, 21.9% had compensated cirrhosis. 9 patients with uremia who underwent dialysis were also enrolled in our study. The demographic and baseline clinical characteristics of the 215 patients are shown in Table 1.

Table 1
Baseline characteristics of patients treated with EBR/GZR

Characteristics	Patients (N = 215)
Sex, male, n (%)	91 (42.1)
Age, years, median (range)	60 (28–87)
Treatment-naïve, n, (%)	207(96.3)
Cirrhosis, n, (%)	47 (21.9)
On dialysis, n, (%)	9(4.2)
History of HCC, n, (%)	1(0.5)
HCV RNA, log_{10}IU/mL, median (range)	6.4 (2.0-8.7)
ALT, U/L, median (range)	36.0(3.0-819.0)
AST, U/L, median (range)	35.0(11.0-705.0)
Total bilirubin, μmol/L, median (range)	14.5 (5.4–57.0)
Albumin, g/L, median (range)	44.6 (23.4–55.4)
PLT,×10^9/L, median (range)	148.0 (11.0-410.0)
α-Fetoprotein, ng/mL, median (range)	5.2(0.6-193.2)
Transient elastography (FibroScan), kPa, median (range)	9.1 (3.3–51.4)
Creatinine μmol/L, median (range)	65.0 (38.9–1058)

Virological response

At EOT,12 weeks and 48 weeks posttreatment, the proportions of all patients with undetectable HCV RNA were 100% (215/215), 99.5% (214/215) and 99.1% (106/107), respectively (Fig. 2). One cirrhosis patient relapsed 12 weeks after treatment with HCV RNA of 3.66*10^5 IU/ml, who had been discontinuing medication for 6 weeks. The overall SVR12 rate was 97.9% (46/47) in patients with liver cirrhosis and 100% in non-cirrhosis patients. By November 30, 2020, a total of 107 patients obtained 48-week follow-up data. One patient with liver cirrhosis recurred 48 weeks after treatment with HCV RNA of 1.00*10^6 IU/ml. She was a non-reinfected patient with the same genotype as the baseline. Virological responses were obtained in all 9 uremic and dialysis patients 12 weeks and 48 weeks after treatment.

Biochemical changes

The ALT, AST, TBIL and Albumin levels and normalization rate of all patients at baseline, EOT,12 and 48 weeks posttreatment are shown in Table 2. The ALT and AST normalization rate with EBR/GZR treatment

increased significantly at EOT,12 weeks and 48 weeks posttreatment compared with the baseline (ALT 91.6%, 96.3%,97.2% vs 59.5%, P□0.01; AST 85.6%,95.3%,95.3% vs 61.4%, P□0.01). At EOT,12 weeks and 48 weeks posttreatment, serum creatinine levels had no significant change compared with the baseline (66.0,65.0,67.0 vs 65.0umol/l, P > 0.05). During the 48-week follow-up, no patients developed decompensated cirrhosis.

Table 2
Levels and normalization rates of ALT, AST and TBIL at baseline, EOT,12 weeks posttreatment and 48w posttreatment

Liver function parameters	**Baseline**	**EOT**	**12 w Posttreatment**	**48 w Posttreatment**
Patients N	215	215	215	107
ALT, U/L, median (range)	36.0 (3.0-819.0)	17.0 (2.0-111.0)	16.0 (3.0-142.0)	15.0 (4.0-105.0)
ALT Normalization rate, n/N (%)	128/215 (59.5%)	197/215△ (91.6%)	207/215△ (96.3%)	104/107△ (97.2%)
AST, U/L, median (range)	35.0 (11.0-705.0)	11.0 (8.0–76.0)	20.0 (5.0–95.0)	21.0 (9.0-107.0)
AST Normalization rate, n/N (%)	132/215 (61.4%)	184/215△ (85.6%)	205/215△ (95.3%)	102/107△ (95.3%)
TBIL,μmol/L, median (range)	14.5 (5.4–57.0)	13.6 (4.0–59.0)	13.7 (3.2–54.0)	13.9 (4.8–48.8)
TBIL Normalization rate, n/N (%)	147/215 (68.4%)	160/215 (74.4%)	162/215 (75.3%)	78/107 (72.9%)
Albumin, g/L, median (range)	44.6 (23.4–55.4)	46.3 (31.7–53.7)	46.6 (32.9–52.6)	46.8 (30.1–52.6)
ALB Normalization rate, n/N (%)	199/215 (92.5%)	212/215 (98.6%)	214/215 (99.5%)	106/107 (99.1%)
Creatinine μmol/L, median (range)	65.0 (38.9–1058)	66.0 (36.0-1134.0)	65.0 (34.0-1144)	67.0 (40.0-1031.0)
△P < 0.01				

Safety and adverse events

In general, our results indicated that the safety of EBR/GZR treatment in HCV-1 patients was tolerable. The overall incidence of AEs was 18.1% (n = 39), which was mild to moderate. One patient was interrupted for 6 weeks due to non-drug factors during treatment. The most frequent adverse events were elevated total bilirubin (7.4%), fatigue (4.7%), dizziness (2.3%) and nausea (2.3%), see Table 3. Severe adverse events and death did not occur in our study.

Table 3
Adverse events occurring during treatment of patients treated with EBR/GZR

Adverse events	Patients, n (%) N = 215
Interruption during treatment	1 (0.5)
Any adverse event	39 (18.1)
Elevated total bilirubin	16 (7.4)
Fatigue	10 (4.7)
Dizziness	5(2.3)
Nausea	5 (2.3)
Itchy skin	2 (0.9)
Weight loss	2 (0.9)
Anemia	1 (0.5)
Serious adverse events	0 (0.0)
Death	0 (0.0)

Discussion

Rapid improvements in hepatitis C virus (HCV) therapy have significantly increased the cure rate of chronic hepatitis C[9, 10]. However, this therapy truly entered the DAA era with its approval in Apr 2018 in China. Epidemiological studies reported that HCV genotype 1 infection was the most prevalent genotype in the world and China[11–13]. As a powerful antiviral regimen for HCV-1b has been demonstrated in clinical studies, there are several reports on the outcomes of EBR /GZR treatment in real-world clinical practice[14–16]; however, there are few reports from the Chinese mainland. Chinses patients in the real world are more heterogeneous and have more complications comparing with those in RCT studies, and there are differences in viral infection pathways, races from other countries such as Europe and the United States, therefore, it is worthwhile for us to discuss the real effect of this regimen on hepatitis C patients in China. This real-world cohort study from the Chinese mainland was aimed to observe the

efficacy and safety of the EBR /GZR for hepatitis C patients, and the liver function in the 1-year follow-up period after treatment.

Through the inclusion of compensatory cirrhosis patients, our study showed that the overall SVR12 rate in patients receiving EBR /GZR was excellent (99.5%) and was slightly higher than the response rates(98.2%)in the clinical trials from the Asia–Pacific region and Russia[6]. Of the 47compensated cirrhotic patients in our study, 100% of patients achieved a virological response at the end of treatment, and 46 patients (97.6%) achieved SVR12, which was similar to the previous real-world studies[14, 17, 18]. Although SVR12 was considered to be hepatitis C virus cure[19], in our study, one cirrhosis patient relapsed 48 weeks posttreatment after receiving SVR12. Long term follow-up of patients with liver cirrhosis after HCV treatment was still necessary.

During the treatment, liver function improved significantly and more than 91% of patients had normal ALT levels at the end of treatment. At 48 weeks posttreatment, 97.2% of patients' ALT levels and 95.3% of patients' AST levels remained normal. We found that overall liver function was relatively stable and there was no progression of decompensated cirrhosis during the 48-week follow-up.

In this study, 9 patients with chronic renal failure and regular dialysis completed 12 weeks of antiviral treatment with EBR /GZR without drug reduction. Previous studies on patients with advanced kidney disease have suggested that EBR /GZR is well tolerated[20]. All 9 patients achieved SVR12 and SVR48 in our study which was consistent with our previous findings[21], indicating that this regimen had good therapeutic effect and tolerance in renal failure patients.

Our data showed the safety and tolerability (including renal safety) of EBR /GZR. One patient discontinued treatment for 6 weeks because of his original disease, while no patient discontinued because of drug interactions. In this study, side effects were reported in 39 patients. Although the reported AE incidence in this study was only slightly higher than that in some real-world studies[15, 16], most of AEs were mild in severity. During treatment, the hyperbilirubinemia observed was the most common adverse event; however, the severity was mainly graded 1 or 2 and lasted only 2–4 weeks for most patients. In general, EBR /GZR was well tolerated and safe in clinical practice.

Since DAA in China has been available in the past year and is expensive, there are few large sample reports about the real-world study. Although this study reflects the real-world data of HCV-1b patients, several limitations existed in our study. First, the patients in this study came from two medical centers, while they were limited in one region and the sample size was small. Second, there was potential bias in the doctor prescriptions and incomplete patient records in the real-world efficacy evaluation. Moreover, our study included patients with chronic hepatitis C and compensatory cirrhosis and lacked data on a large sample of cirrhotic patients.

Conclusion

In conclusion, in this real-world study, 12-week Elbasvir /Grazoprevir was shown to achieve a high SVR12 of 99.5% in Chinese patients with genotype-1b hepatitis C and maintain 99.1% at 48 weeks posttreatment. Liver function improved after treatment and during the 48 weeks posttreatment. Elbasvir /Grazoprevir therapy, with excellent efficacy and tolerance, is an effective therapeutic option for patients with chronic hepatitis C and compensatory cirrhosis.

Abbreviations

CHC chronic hepatitis C; DAA direct-acting antiviral drug; EBR Elbasvir; GZR Grazoprevir; HCV hepatitis C virus; SVR sustained virologic response; EOT end of treatment; AEs adverse events; SAEs serious adverse events; ALT alanine aminotransferase; AST aspartate aminotransferase; TBIL total bilirubin; ALB Albumin

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tianjin Third Central Hospital and informed consent was obtained from all patients prior to study initiation.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors's contributions

LJ and ZYP contributed equally to this work. LJ, WFM and TH designed the research. LJ and ZYP drafted the manuscript. LJ and ZYP collected the data and established the database. YYC and FL presided over the enrollment and exclusion of the research subjects. LF, XH, LHM, XHL, YYK, LTH, LL and LCZ managed and followed up the patients. LJ analyzed the data statistically. WFM and TH participated in paper modification and revised the manuscript for English writing. All authors read and approved the final manuscript.

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Not applicable

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Figures

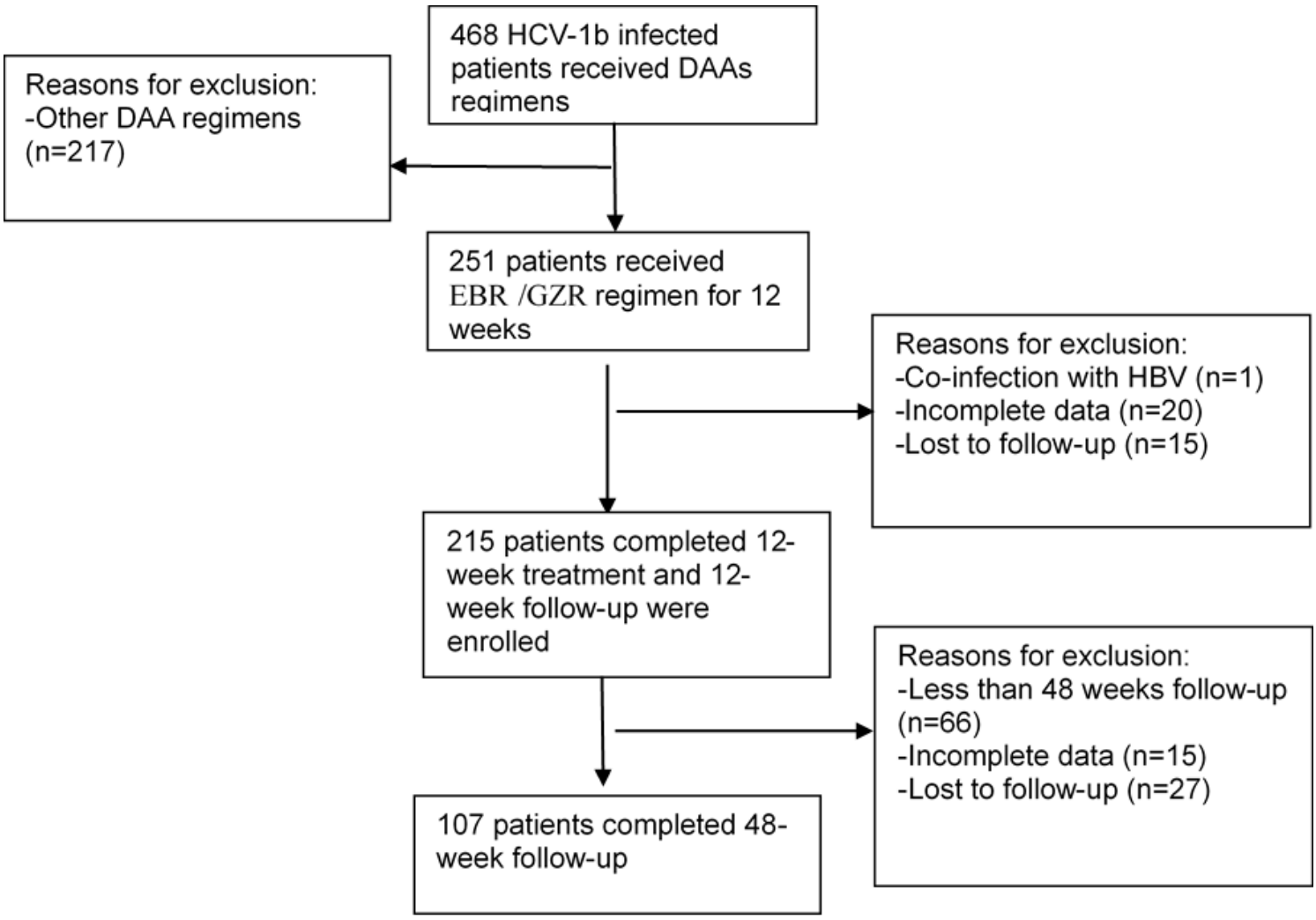

Figure 1

Patient recruitment flowchart

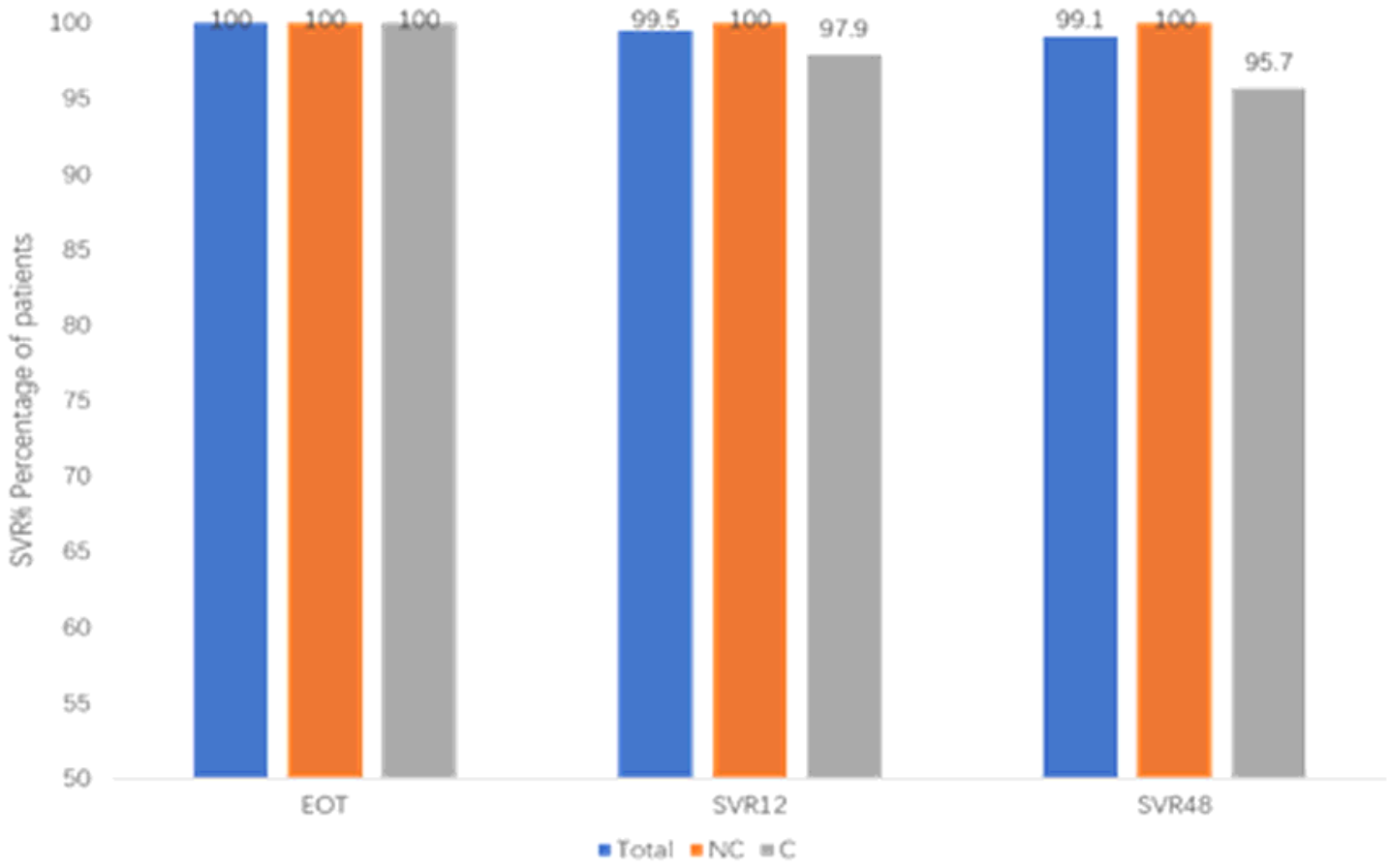

Figure 2

Percentage of patients with HCV RNA< Lower Limit of Detection