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Original Research Article.

The Efficacy and Safety of the Combination of Elbasvir/Grazoprevir In the Treatment of Chronic Hepatitis C Virus Infection: A Systematic Review of Clinical Trials

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ABSTRACT

Elbasvir (EBR) and grazoprevir (GZR) are new direct-acting antivirals for patients with hepatitis C virus (HCV) infection. This systematic review aimed to investigate the efficacy and safety of this dual-drug combination in HCV infection. Four electronic search engines/libraries were systematically searched for relevant publications. Studies were screened for eligibility and data were extracted. Sustained virologic response rate after 12 weeks of treatment (SVR12) and commonly reported outcomes were discussed. The databases search picked up 597 and nine papers were finally included for our study after screening. Included clinical trials were either double-blind or open-label trials. The majority of which are phase III and are part of the C-EDGE trial program. The results of the qualitative synthesis proved the high efficacy of once-daily EBR/GZR 50/100 mg in patients with chronic HCV infection, including difficult to treat populations. Higher SVR 12 was achieved in the different groups in the included clinical trials mainly for HCV genotype1 and genotype 4 infections. EBR/GZR was generally well tolerated in clinical trials. Fatigue was the most common reported adverse event. This study showed that EBR/GZR is an effective new treatment of adults with chronic HCV infections mainly genotype 1 and 4 infection, including the difficult-to-treat patient populations. We recommend further well designed controlled trials to assert upon these results.

Keywords: Elbasvir, EBR, Grazoprevir, GZR, HCV, SVR12, Systematic Review.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem with 130-150 million people affected and 700 000 people die each year due to HCV-related complications as chronic HCV can lead to cirrhosis, hepatocellular carcinoma, and hepatic decompensation.[1-3] However, effective treatment has proved to reduce long-term liver-related complications and mortality.

The management therapy of this chronic disease is changing along the years. The interferon (IFN)-based regimens has been used for the treatment of HCV, but the severe adverse events (AEs) and their way of administration reduced the patients' compliance to the treatment.[4] Other than interferon, newer regimens has been used as direct-acting antiviral (DAA) agents. The development of DAA agents has been introduced to offer improved efficacy and tolerability and allowing the ability to use IFN-free regimens for HCV.[5-9] However, HCV therapy that is still needed to be of shorter duration, with a good barrier to resistance, and highly effective for end-stage renal disease patients and other difficult-to-treat populations.

Recently, The combination of elbasvir (EBR), a once-daily NS5A inhibitor, and grazoprevir (GZR), a once-daily HCV NS3/4A protease inhibitor, is approved by the US Food, and Drug Administration, EU and Japan, Australia, Saudi Arabia, Israel,

Switzerland and Canada for the treatment of chronic HCV genotype1(GT1) or genotype 4 (GT4) infection.[10-12]

In vitro, the combination has been highly potent against HCV different genotypes.[13] It retains substantial activity against resistance-associated variants (RAVs) commonly detected after failed therapy with first-generation protease inhibitors and even in the presence of RAVs associated with failure of other NS5A inhibitors, as daclatasvir and ledipasvir.[14,15] Moreover, Corman et al.[16] reported that EBR/GZR was the economically dominant regimen for treating GT1 patients, and was cost saving in all other populations compared with other oral DAA agents. In an integrated study of the safety and efficacy of this drug combination, it showed to be effective and safe in HCV GT1/4 treatment.[17] In addition, a new retrospective study showed that the drug therapy for 12 weeks offers an effective management choice for patients with HCV Genotype 1b infection. Also, SVR12 was high in patient's subgroups, even participants with compensated cirrhosis, and increased baseline viral load.[18] Furthermore; many other clinical trials have investigated the safety and efficacy of the combination for HCV patients with different associated diseases, conditions and groups of patients. Therefore, the aim of this systematic review is to build a concrete evidence asserting the efficacy and safety outcomes of the dual-drug combination of EBR/GZR in treatment of HCV infection considering the different variables and comparisons in the different conducted clinical trials.

METHODS

Search Strategy: We established the protocol and four electronic search engines/libraries were systematically searched for relevant publications, including PubMed, Scopus, Web of Science, and Cochrane library. The search string for all libraries was as follows: (Elbasvir OR MK-8742) AND (Grazoprevir OR MK-5172) AND ("Hepatitis C virus" OR HCV). Additionally, we conducted a manual search by reviewing the citations within the included publications and reviewing the related references presented in PubMed and related journals.

Selection Criteria and Title and Abstract Screening

Search results from the four-aforementioned-search databases were imported into Endnote X7 (Thompson Reuter, CA, USA) for automatic duplicates deletion. Two reviewers independently screened the references using the predetermined eligibility criteria which focused on the inclusion of any clinical trial reporting the efficacy and safety of using the combination of EBR/GZR, for the treatment of HCV infection. No restrictions were implied on specific language, publication year, place, age, or gender of the patients. Besides studies with unreliable extracted data, we excluded book chapters, abstract-only articles, conference papers, reviews, theses, posters, editorials, and letters. Any discrepancies in screening step was discussed between the two reviewers to reach the consensus. Consultation from third reviewer was acquired if necessary. The full-text screening was subsequently conducted to identify relevant references for data extraction.

Data Extraction

The data-extraction-sheet template was initially developed through a pilot trial with the most three relevant references. Two researchers then independently extracted the data into the template. Extracted data included: basic and demographic data, efficacy and safety outcomes.

Risk of Bias Assessment

The risk of bias in each included study was independently assessed by two reviewers using the Cochrane Collaboration's tool for assessing risk of bias.[19] It is a two-part tool, addressing seven specific domains, including: randomization, allocation concealment, blinding of subjects, blinding of outcome assessors, reporting of incomplete outcome data, selective outcome reporting, and other potential sources of bias. In each domain, each study took one of three categories; 'low risk,' 'high risk,' or 'unclear risk' of bias. Any disagreement was resolved by discussion between two reviewers and by consultation from a third reviewer to reach the consensus.

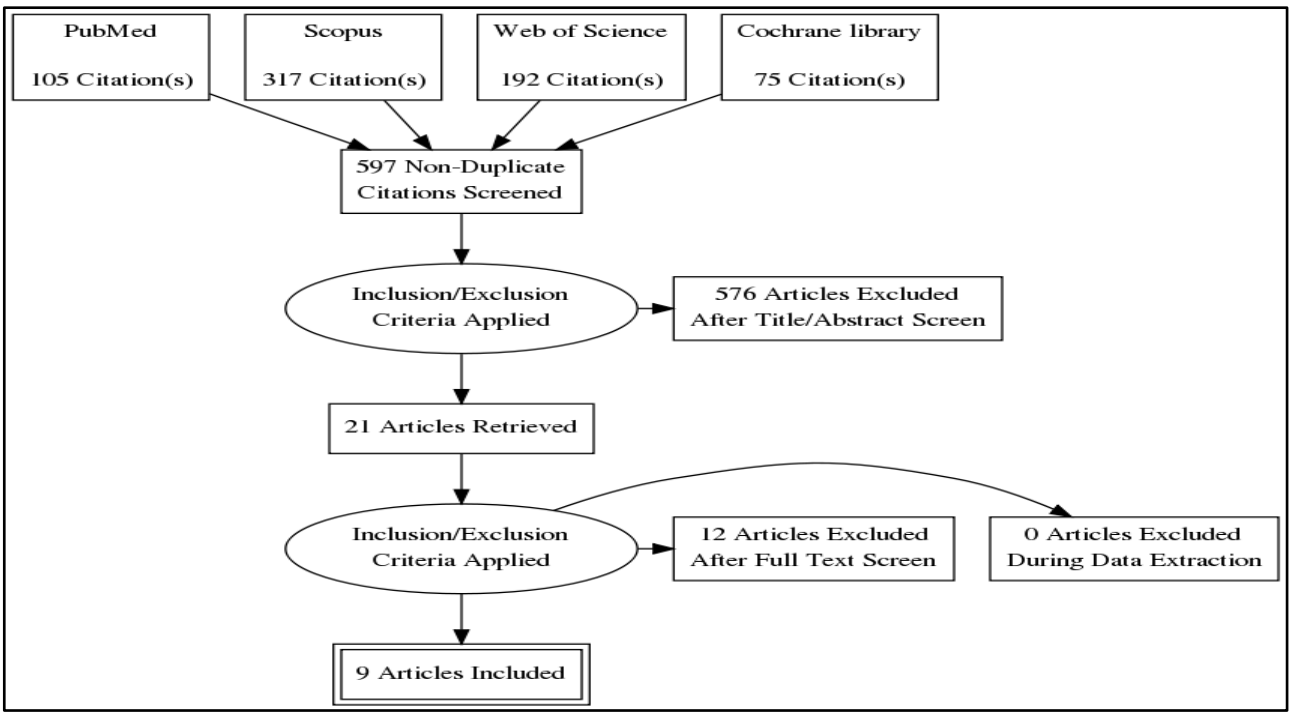

Fig.1: PRISMA flow diagram explaining the cascade of searching several databases, removal of duplicates, screening steps, and reviewing processes

Table 1: Summary of included Populations and results for Phase II and Phase III GZR and EBR clinical trials

Study ID	Combination (Duration per week)	N	Population genotype and characteristics	SVR 12
C-WORTHY (8 vs 12 weeks) Sulkowski et al., 2015	**EBR/GZR (8)**	30	TN; HCV GT 1a-infected, non-cirrhotic	80%
	EBR/GZR+RBV(12)	85	TN; HCV GT 1a/1b-infected, non-cirrhotic	93%
	EBR/GZR (12)	44	TN; HCV GT 1a/1b-infected, non-cirrhotic	98%
	EBR/GZR+RBV(12)	29	TN; HIV/HCV GT 1a/1b-coinfected, noncirrhotic	97%
	EBR/GZR (12)	30	TN; HIV/HCV GT 1a/1b-coinfected, noncirrhotic	87%
C-WORTHY (12 vs18 weeks) Lawitz et al., 2015	**EBR/GZR+RBV(12)**	31	TN; HCV GT 1-infected cirrhotic patients	90%
	EBR/GZR (12)	29	TN; naïve HCV GT 1-infected cirrhotic patients	97%
	EBR/GZR+RBV(18)	32	TN; naïve HCV GT 1-infected cirrhotic patients	97%
	EBR/GZR (18)	31	TN; naïve HCV GT 1-infected cirrhotic patients	94%
	EBR/GZR+RBV(18)	32	Patients with previous null response to Tretment with Peg IFN/RBV and are HCV GT 1-infected ± cirrhosis	94%
	EBR/GZR (12)	33	Patients with previous null response to treatment with Peg IFN/RBV and are HCV GT 1-infected ±cirrhosis	91%
	EBR/GZR+RBV(18)	33	Patients with previous null response to Treatment with Peg IFN/RBV and are HCV GT 1-infected ±cirrhosis	100%
	EBR/GZR (18)	32	Patients with previous null response to Treatment with Peg IFN/RBV and are HCV GT 1-infected ± cirrhosis	97%
C-EDGE TE Kwo et al., 2017	**EBR/GZR (12)**	105	Patients who previously failed Treatment with Peg IFN/RBV and are HCV GT 1, 4, 6-infected ± cirrhosis	92.4%
	EBR/GZR+RBV(12)	104	Patients who previously failed Treatment with Peg IFN/RBV and are HCV GT 1, 4, 6-infected ± cirrhosis	94.2%
	EBR/GZR (16)	105	Patients who previously failed Treatment with Peg IFN/RBV and are HCV GT 1, 4, 6-infected ± cirrhosis	92.4%
	EBR/GZR+RBV(16)	106	Patients who previously failed Treatment with Peg IFN/RBV and are HCV GT 1a/1b, 4, 6-infected ±cirrhosis	98.1%
C-EDGE CO Rockstroh et al., 2015	**EBR/GZR (12)**	218	TN; HIV/HCV GT 1, 4, 6-coinfected ± cirrhosis	95%
C-EDGE TN Zeuzem et al., 2015	**EBR/GZR (12)**	316	TN; HCV GT 1, 4, 6 ± cirrhosis	95%
C-SURFUR Rothe et al., 2015	**EBR/GZR (12)**	122	TN/TE; HCV GT 1 with CKD Stage 4/5 ± on HD ± cirrhosis	94%
C-EDGE IBLD Hezode et al., 2017	**EBR/GZR (12)**	107	TN/TE; GT 1, 4 or 6; IBLD ± HIV co-infection ± cirrhosis	93.5
C-EDGE COSTAR Dore et al., 2016	**EBR/GZR (12)**	201	TN; GT 1, 4 or 6; receiving OAT ± cirrhosis	94
Japanese Trial Kumada et al., 2017	**EBR/GZR (12)**	227	TN/TE; GT 1 without cirrhosis	96.5%

GZR= Grazoprevir; EBR= Elbasvir; RBV= Ribavirin; SVR= Sustained Virological Response; SVR12= proportion of patients achieving HCV RNA less than 15 IU/mL 12 weeks after end of treatment; GT= genotype; DAA = direct acting antiviral. CKD chronic kidney disease; IBLD inherited blood disorders; OAT opioid-agonist therapy, PegIFN pegylated interferon, RBV ribavirin, TE treatment experienced, TN treatment-naive

RESULTS

Selection and Characteristics of the Included Studies

The databases search picked up 597 after the removal of 92 duplicates by the EndNote software. Of them, title and abstract screening excluded 576, then full-text screening excluded 12 articles based on our inclusion and exclusion criteria. We finally included nine papers for our study.[20-28] (fig. 1). Included clinical trials were either double-blind or open-label trials and the majority of which are phase III and are part of the C-EDGE trial program. The comparisons of the included studies populations are summarized as part of Table 1.

Risk of Bias

The overall assessed risk of bias was moderate to high in the most of the studies. We provided a summary for the included trials risk of bias in fig. 2

Therapeutic Efficacy of Elbasvir/Grazoprevir

The included studies reported the efficacy of once-daily EBR/GZR 50/100 mg in patients with chronic HCV infection, with or without compensated cirrhosis with different groups included and some studies targeted difficult to treat populations. Table 1 provided a summary for different regimens and their achieved SVR 12.

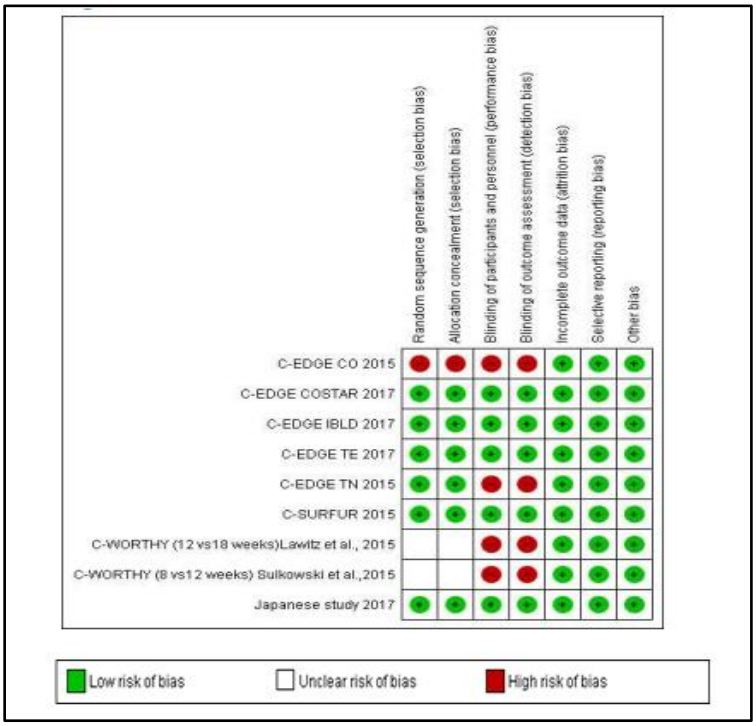

Figure 2: The risk of bias assessment of the included studies (Using RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK).

Table 2: Adverse events for Phase II and Phase III GZR and EBR clinical trials

Study ID	Patients with SAEs, n(%)	Discontinuation, n (%)	Deaths, n (%)	Common AEs, n (%)				Hemoglobin (<10.0 g/dL)
				Fatigue	Headache	Nausea	Diarrhea	
C-WORTHY (8 vs 12) n=218	3 (1)	6 (2.8)	0 (0)	51 (23)	44 (20)	32 (15)	21 (10)	11 (<1)
C-WORTHY (12 vs 18) n=253	7 (3))	2 (1)	1(<1)	66 (26)	58 (23)	---	--	12 (<1)
C-SURFER n=111	16 (14.4	0 (0)	1 (0.9)	11 (9.9)	19 (17.1)	17 (15.3)	6 (5.4)	4 (3.6)
C-EDGE CO n=218	2 (1)	0 (0)	0 (0)	29 (13)	27 (12)	20 (9)	16 (7)	0 (0)
C-EDGE TN n=316	9 (3)	3 (0.9)	2 (0.5)	49 (16)	52 (17)	28 (9)	---	3 (0.7)
C-EDGETE n=420	14 (3.3)	7 (1.7)	0 (0)	97 (23.1)	83 (19.8)	46 (11.0)	---	31 (7.4)
C-EDGE IBLD n = 107	3 (2.8)	0 (0)	0 (0)	23 (21.5)	18 (16.8)	9 (8.4)	---	41 (38.4)
C-EDGE COSTAR n=201	7 (3.5)	1 (0.5)	0 (0)	32 (15.9)	25 (12.4)	22 (10.9)	---	1 (0.5)
Japanese patients *n* = 227	11 (4.8%)	3 (1.3%)	0 (0.0%)	---	---	---	---	---

AE= Adverse Event SAE= Serious Adverse Event, CO= co-infected with HCV/HIV; TN= Treatment Naïve;
TE= Treatment Experienced, IBLD inherited blood disorders

C-WORTH[24,27] was a phase 2 randomized, open-label study in which patients with GT1 or 3 infections were included. The patients were either treatment-naïve or who had failed prior therapy with Peg- IFN ± ribavirin and were randomized in a 1:1 ratio to EBR/GZR with or without ribavirin for 8 weeks while evaluating the shorter duration of therapy in subjects with

genotype 1b infection without cirrhosis. Moreover, patients were randomized to EBR/GZR with ribavirin (RBV) for 12 or 18 weeks while evaluating subjects with genotype 3 infection without cirrhosis who were treatment-naïve. Otherwise, patients with genotype 1 infection with or without cirrhosis who were treatment-naïve (with or without HCV/HIV-1 co-infection) or who were Peg-IFN+ RBV null responders, were randomized to EBR/GZR with or without ribavirin for 8, 12 or 18 weeks. In HCV genotype 1 patients, with or without HIV co-infection, the SVR after 12 weeks of treatment was high in mono infected HCV patients and less higher in HCV/HIV co-infected patients.

It's important to note that for mono-infected patients treated for 8 weeks, the SVR rate was 80% with a higher rate of post treatment virologic failure (17%) than the overall failure of 4% in the 12-week arms.

In difficult to treat patients with HCV genotype 1 infection who are naïve of antiviral therapy and cirrhotic or who are previous null responders to Peg-IFN+ RBV with or without cirrhosis, the SVR was up to high when using the combination of EBR/GZR with or without ribavirin for 12 or 18 weeks. In patients infected with genotype 3, EBR/GZR ± RBV were less effective with a breakthrough in 17 out of 41 patients.

C-EDGE co-infection[25] was an open-label phase 3 study of treatment-naïve HCV/HIV-1 co-infected patients with genotype 1, 4, or 6 infections with or without cirrhosis. The subjects received EBR/GZR for 12 weeks. Patients were either naive to treatment with any antiretroviral therapy (ART) or stable on ART for at least 8 weeks. All patients received grazoprevir 100 mg plus elbasvir 50 mg in a fixed-dose combination tablet once daily for 12 weeks. HCV genotype 1/HIV co-infected patients who received EBR/GZR for 12 weeks achieved an SVR of 96%. Only 28 HCV genotype 4 and 2 HCV genotype 6 patients were included.

C-Surfer[26] was the first randomized, placebo-controlled phase 3 study to evaluate an all-oral, ribavirin-free regimen in HCV genotype 1 infected patients, with or without cirrhosis, with Stage 4 or Stage 5 advanced chronic kidney disease (CKD), including patients on hemodialysis. Patients, who were treatment-naïve or who had failed prior therapy with peg- IFN or peg-IFN± ribavirin therapy, were randomized to receive EBR/GZR 100/50 mg or a placebo for 12 weeks. The SVR in patients who received EBR/GZR was 99%. Adjustments of EBR/GZR dose are not needed in patients with non-dialysis-dependent stage 4–5 chronic kidney disease as less than 1% of EBR/GZR is renally excreted and thus dose.

In a Japanese study[29], Patients without cirrhosis were randomized to receive EBR/GZR or placebo for 12 weeks, and patients with compensated cirrhosis received open-label EBR/GZR for 12 weeks.Treatment with elbasvir plus grazoprevir was associated with high SVR12 rates in non-cirrhotic patients. The rate of virological failure was low with no on-treatment virological breakthroughs. Moreover, in cirrhotic patients, SVR12 rates were 97%, with low rates of virological failure.

The C-EDGE IBLD[21] trial aimed to investigate the efficacy of EBR/GZR in HCV-infected adults with various inherited blood disorders (IBLDs), including sickle cell anaemia, b-thalassaemia, and von Willebrand disease/haemophilia A or B. Treatment with EBR/GZR for 12 weeks was associated with high overall rates of SVR12 in the immediate-treatment group of this trial. The lowest SVR12 rates (both 83.3%) were evident in patients co-infected with HIV and Asian patients; however, these subgroups contained only a small number of patients (both n = 6).

C-EDGE TN[28] investigated EBR/GZR therapy for 12 weeks in treatment naive adults without HIV co-infection and treatment was associated with a high rate of SVR12. Among 421 participants, 382 (91%) had genotype 1 infection, and 92 (22%) had cirrhosis. Of 316 patients receiving immediate treatment, 299 of 316 achieved 95% SVR12, including 144 of 157 with genotype 1a (92%), 129 of 131 (99%) with genotype 1b, 18 of 18 (100%) with genotype 4, 8 of 10 (80%) with genotype 6, 97%with cirrhosis, and 231 of 246 (94%) without cirrhosis. Virologic failure occurred in 13 patients (4%), including 1 case of breakthrough infection and 12 relapses, and was associated with baseline NS5A polymorphisms and emergent NS3 or NS5A variants or both.

The C-EDGE COSTAR[20] investigated the efficacy of 12 weeks of treatment with EBR/GZR in patients with chronic HCV who had been receiving opioid agonist

therapy) OAT(for above 3 months with above 80% adherence to OAT visits. Patients actively using drugs of potential abuse were included. EBR/GZR treatment for 12 weeks was associated with high overall SVR12 rates in the immediate treatment group, which were consistent across genotype 1a, 1b and 4.

The C-EDGE TE[23], a phase 3 randomized controlled open-label trial to assess the effects of 12 or 16 weeks of treatment with EBR/GZR for patients infected with hepatitis C virus (HCV) genotype 1, 4, or 6, with or without cirrhosis, previously treated with peg-interferon and ribavirin, with or without twice-daily ribavirin, in this patient population, with 12 weeks of treatment, an SVR12 was achieved by 92.4% of patients given EBR/GZR and 94.2% of patients given EBR/GZR with RBV. With 16 weeks of treatment, an SVR12 was achieved by 92.4% of patients given EBR/GZR and 98.1% of patients given EBR/GZR with RBV.

Adverse Events

The adverse events (AE) observed in patients treated with EBR/GZR for 12 weeks were mild in severity, and the most common AE reported was fatigue. The proportion of subjects who permanently discontinued treatment due to AE was <1%. Overall, EBR/GZR was generally well tolerated in the included clinical trials**. Table 3** summarizes the rates of different AEs with different drug durations.

DISCUSSION

In phase 2, 3 trials, treatment with EBR/GZR, for 12 or 16 weeks achieved high SVR12 rates in treatment-naive and -experienced patients with chronic HCV infection, including patients with HIV co-infection, IBLDs, CKD, patients receiving OAT or of Japanese origin. The efficacy of EBR/GZR was not affected significantly by compensated cirrhosis status. However, the presence of baseline NS5A polymorphisms appeared to impact SVR12 rates. The combination may not be effective for HCV GT 3 patients. Moreover, EBR/GZR was generally well tolerated in clinical trials, and the most common AE reported was fatigue.

These results is constant with European Association for the Study of the Liver (EASL) guidelines which recommend 12 weeks of EBR/GZR as an option for treatment-naive and -experienced patients with chronic HCV genotype 1a, 1b and 4 infection, with or without cirrhosis or HIV co-infection.[30] Similarly, current AASLD/IDSA guidelines recommend 12 weeks of EBR/GZR as an option for patients with chronic HCV genotype 1a, 1b or 4

infection, with or without compensated cirrhosis, who are treatment-naive or –experienced.[31] EASL and AASLD/IDSA recommended other DAA regimens include sofosbuvir/ ledipasvir and sofosbuvir/velpatasvir for HCV genotype 1a, 1b or 4 infection.[30,31] Moreover, EASL recommended sofosbuvir plus daclatasvir for patients with HCV genotype 1a, 1b and 4 infections while AASLD/IDSA recommended it for HCV genotype 1a, 1b only. Other recommendations include ombitasvir/ paritaprevir/ ritonavirplus dasabuvir for HCV genotype 1a and 1b infection, and ombitasvir/paritaprevir /ritonavir for HCV genotype 4 infection.

It is noteworthy that The C-EDGE HEAD-TO-HEAD trial[32] showed that EBR/GZR was more effective than sofosbuvir/pegylated IFN (pegIFN)/ RBV in treatment-naive or pegIFN-RBV-experienced adults with HCV, but we did not include it in our study as pegIFN-ribavirin regimens are no longer recommended. There were a baseline NS3 resistance associated variants (RAVs) in patients with HCV genotype 1a and 1b infection in the different trials. However, EBR/GZR was generally associated with high rates of SVR12 in these trials.

To recapitulate, This study showed that EBR/GZR is an effective new treatment of adults with chronic HCV infections mainly genotype 1 and 4 infection, including the difficult-to-treat patient populations with compensated cirrhosis, previous treatment experience, HIV co-infection, IBLDs, CKD or receiving OAT. We recommend further well designed controlled trials to assert upon these results.

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