The efficacy of Elbasvir/Grazoprevir fixed-dose combination for 8 weeks in HCV treatment and health-related quality of life (HRQoL) in treatment-naïve, non-cirrhotic, genotype 4-infected patients (ELEGANT-4): A single-center, single-arm, open-label, phase 3 trial

Ahmad AlEid, Areej Al Balkhi, Adel Qutub, Shahem Abbarh, Abed AlLehibi, Abdullah Almtawa, Nawwaf Al Otaibi, Ahmed AlGhamdi, Adel AlGhamdi, Abdulrahman Alamr, Shameem Ahmad, Khalid Al Sayari, Bashaa Al Ibrahim, Abdullah AlKhathlan
Department of Gastroenterology and Hepatology, King Fahad Medical City, Riyadh, Saudi Arabia

Abstract

Background: Cost, adverse events, and long treatment duration can be significant obstacles in treating hepatitis C virus (HCV)-infected individuals. Shortening the treatment regimen can minimize these barriers, thereby enhancing adherence and increasing medication availability to more patients.

Methods: This is a single-centre, single-arm, open-label, phase 3 clinical trial on treatment naïve, non-cirrhotic, HCV genotype 4 patients. The study aimed to evaluate an 8-week course of Elbasvir (ELB)/Grazoprevir (GZR) in this population. The primary endpoint was sustained virologic response at 12 weeks after the end of treatment (SVR-12). The secondary endpoints were SVR-4, adverse events, and changes in health- and hepatitis-related quality of life (HRQoL).

Results: Of the 30 patients who were enrolled, 29 (97%) achieved SVR-12 and SVR-4 (95% CI: 90-100%). No patients experienced serious or life-threatening adverse events (AEs), but mild/moderate AEs were reported by 16 (53%). The most commonly reported AEs were itching/skin rash (20%), headache (16.7%), abdominal/epigastric pain and decreased appetite (13.3% each), and nausea/vomiting (10%). Marked improvements in HRQoL were reported between the first (baseline) and third (SVR-12) timepoints. HRQoL score improvements involved the physical, mental, and hepatitis-specific indices, and ranged between 6 and 42 points (out of 100, \( P \leq 0.003 \)).

Conclusion: The trial provides empirical evidence that HCV genotype 4-infected patients can achieve viral eradication with an 8-week-regimen of ELB/GZR. Further, this course of treatment is associated with a...
INTRODUCTION

Viral hepatitis is a burden that threatens public health worldwide.\(^1\) Between 1990 and 2013, deaths due to viral hepatitis increased by 63%, with hepatitis B and C infections accounting for 96% of the disease-related mortality. Morbidity, as estimated in disability-adjusted life years (DALYs), also increased from 0.65 million years in 1990 to 0.87 million in 2013. Among the five viruses that cause hepatitis, hepatitis C infection (HCV) was responsible for the largest increase in DALYs (43%).\(^2\)

The prevalence of HCV has decreased over time. In a large 2015 modelling study, liver-related and all-cause mortality in HCV-infected individuals had a significant contribution to the decrease in the disease prevalence. However, the study forecasted a continual decline in global HCV infections, not only because of HCV-related deaths, but also because countries continue to develop national strategies to prevent and treat new and existing cases.\(^3\) One of the most crucial components of successful elimination strategies is adopting effective treatment regimens. When it comes to the treatment of hepatitis C, significant advances were made since 2011 with the development of direct-acting antivirals (DAAs). DAAs rapidly replaced the interferon-based regimens, and were used to treat two-thirds of the 950,000 patients who received treatment in 2015. Sustained virologic response, which in HCV terms, is considered an equivalent to virologic cure, was achieved in around 700,000 patients of those who were treated.

The World Health Organization (WHO)’s Eastern Mediterranean region is the most affected area by HCV. In 2017, it was estimated that chronic hepatitis C (CHC) had a prevalence of 2.3% in the Middle East.\(^4\) While most cases were attributed to the endemic countries in the region like Egypt and Syria, Saudi Arabia was predicted to have a population of 105,000 HCV-infected individuals (95% confidence interval [CI] in thousands: 79-189).\(^5\) HCV genotype 4 (GT-4) was the most common of the six HCV genotypes, accounting for 52.6% of the total infections.

Despite the relatively low numbers of infected individuals in Saudi Arabia, HCV remains a challenge in the country. However, one of the main obstacles in treating patients on a large scale is the high cost of the current treatment regimens. Multiple approaches to this issue have been proposed, among them, a shortened treatment course of 6–8 weeks instead of the standard 12 weeks. The strategy of shortening the treatment can help in reducing the cost from 50% to 33%, ultimately increasing its availability to more patients.

Multiple DAA-based regimens have been in use for HCV treatment since 2014. Among them are Sofosbuvir/Velpatasvir, which is effective in a broad range of HCV-infected patients when given for 12 weeks and Glecaprevir/Pibrentasvir, which is the only 8-week-regimen approved for HCV treatment.\(^6\) Another 12-week-regimen that is commonly used in HCV patients is Elbasvir (EBR)/Grazoprevir (GZR), which are two potent inhibitors of non-structural protein 5A (NS5A) and NS3/4A serine protease, both of which are enzymes that play a role in HCV replication, virion assembly, and blocking the effects of interferon-alpha in human cells.\(^6-9\) In this single-center, single-arm, open-label, phase 3 trial we evaluated the efficacy of a shortened course of EBR/GZR (8 weeks instead of the standard 12 weeks) in patients who are treatment naïve, non-cirrhotic and mono-infected with HCV genotype 4.

PATIENTS AND METHODS

ELEGANT-4 was a single-arm, open-label, phase 3 clinical trial on 30 patients, in a single, tertiary care center in Riyadh, Saudi Arabia. The study was conducted in compliance with the latest version of the Declaration of Helsinki, after obtaining the approval of the hospital’s Institutional Review Board (IRB). All patients provided written consent after reading the study procedure and having the other treatment options explained to them. Further, all authors had access to the study data and reviewed the final manuscript prior to publication.

Due to lack of evidence on the effects of an 8-week course of ELB/GZR on patients with HCV genotype 4, this trial evaluated its clinical outcomes under ideal conditions (efficacy study). Accordingly, the eligibility criteria were highly selective of patients with healthier
conditions and better chances to respond to HCV therapy.

Eligibility
Adults (age ≥18 years) who were competent to provide informed consent, living in Saudi Arabia during the study period, were naïve to HCV treatment, had no advanced fibrosis, and were infected with HCV genotype 4, were eligible to participate. Advanced fibrosis was defined by a transient elastography result of more than or equal to 9.6 kPa, or fibrosis stage F3 or F4 on the METAVIR scoring system. Patients who were co-infected with Human Immunodeficiency Virus (HIV) or hepatitis B virus (HBV) were excluded from the study. Other excluded groups were organ transplant recipients, patients who had type 2 or 3 cryoglobulinemia with end-organ manifestations, and patients with proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis. Pregnant patients and those with hepatocellular carcinoma were also excluded. Finally, patients were asked about their medications to evaluate potential interactions with the study drug. The University of Liverpool drug interaction database was used for this purpose. In this database, the interactions are divided into three categories; major, mild/moderate, and none. Any medications with major or mild/moderate interactions were discontinued or replaced with alternatives that had no interactions with the study drug. When no alternatives were available, the patient was excluded from the study.

Baseline evaluation and treatment regimen
After obtaining their written informed consent, participants received a treatment regimen that consisted of a single, daily oral tablet of Elbasvir 50 mg and Grazoprevir 100 mg for 8 weeks. At baseline, the patients were evaluated clinically and with laboratory tests that included complete blood count, liver enzymes, bilirubin, serum creatinine, urea, electrolytes, and international normalized ratio (INR). Additionally, assessment of the patients’ quality of life was done using the second version of the Hepatitis Quality of Life Questionnaire (HQLQ™, Version 2).[10]

Follow-up and monitoring
Participants were followed up over three visits afterwards; one at four weeks while on treatment, one at four weeks after the end of treatment, and one at 12 weeks after the end of treatment. Each visit included a repeat set of the aforementioned laboratory investigations and a clinical evaluation of adverse events. Adverse events were considered major if they matched grades 3, 4, or 5 on the Common Terminology Criteria for Adverse Events (CTCAE 5.0), and minor if they matched grades 1 and 2. Quality of life questionnaires were given to the participants twice after the baseline evaluation; once while on treatment, and another time 12 weeks after completion of treatment.

The Hepatitis Quality of Life Questionnaire
The HQLQ consisted of a physical health component (PCS), a mental health component (MCS), a self-evaluated health transition item (SET), and four hepatitis-specific items. The latter included general health distress (HD), psychological well-being (PWB), hepatitis-specific functional limitations (HLIM), and hepatitis-specific health distress (HHD) scales. Higher scores on each component/scale represent more favorable results (e.g., better physical, emotional, and psychological functioning, and little to no limitations in these aspects). Higher scores on the self-evaluated transition item, however, represent less favorable results.

Endpoints
The primary endpoint was the achievement of sustained virologic response (SVR) at 12 weeks after the end of therapy.[11] In this trial, SVR was defined at HCV RNA below the level of detection (<15 IU/mL). The secondary endpoints included the achievement of SVR at 4 weeks after the end of treatment (SVR-4), number of patients with adverse events, and changes in quality of life from the baseline while on treatment and after the end of treatment.

Statistical analysis
Statistical analysis was performed using the IBM SPSS Statistics 26™ package. Categorical outcomes were expressed in frequencies, percentages, and 95% CIs where applicable, while continuous variables were expressed in means and standard deviations (SD). The HQLQ score distribution was tested for normality, then compared between the three time points (i.e., baseline, while on treatment and 12 weeks after the end of treatment) using the one-way Analysis of Variance (ANOVA) on ranks (Kruskal–Wallis H test). Comparisons between each two time points were carried out using Wilcoxon signed-rank test. The two-tailed P values were reported and considered significant if <.05.

RESULTS
Throughout the trial period, 30 patients (19 females) were enrolled. The ages of the participants ranged between 21 and 74 years (mean ± SD: 44 ± 13 years), their baseline viral loads ranged between 26 and 20 + million IU/mL and they were mostly asymptomatic (70%) at presentation. For those who had symptoms, the most
common presenting complaints were fatigue (13%), loss of appetite (6.7%), weight loss (6.7%), and abdominal/right upper quadrant pain (6.7%). Other symptoms included sleep disturbances (i.e., insomnia, hypersomnia) (6.7%), bloating (6.7%), change in bowel habits (i.e., diarrhea or constipation) (6.7%), itchy skin/tingling (6.7%), vomiting (3.3%), dizziness (3.3%), and arthralgia (3.3%). The participants’ baseline and laboratory characteristics and their changes over the study period are shown in Table 1.

Continued absence of detectable viral RNA for 12 weeks after the end of therapy (SVR-12) was achieved in 29/30 (97%) of the participants (95% CI: 90-100%). Similarly, absence of HCV RNA for 4 weeks after the end of treatment (SVR-4) was achieved in 29/30 patients (97%). For 27/30 patients (90%), HCV RNA went below the level of detection by the time they completed 4 weeks on treatment (95% CI: 79-100%). However, all three patients whose viral loads were detectable at 4 weeks ended up achieving SVR-4 and SVR-12. A flowchart of the patients’ progress in achieving SVR-related outcomes is shown in Figure 1.

While on treatment, no patients experienced severe or life-threatening adverse events (CTCAE grades 3–5). However, 16 patients (53%) reported having CTCAE grades 1–2 adverse events. Of those, six patients (20%) reported skin rash/itching, five (16.7%) reported headache, four (13.3%) reported abdominal/epigastric pain, three (10%) reported decreased appetite and three (10%) reported nausea/vomiting. Less frequent adverse events included weight loss, dizziness, and depression/insomnia (each reported by 3.3% of patients). While all patients who presented with fatigue at baseline improved while on treatment, one patient (3.3%) complained of new-onset fatigue that was temporally associated with the medication. Headache was the most persistent adverse event after the end of therapy. Of the five patients who reported having headaches while on treatment, four continued to have them for 4 weeks after they stopped taking it. Nevertheless, other than one patient who continued to experience mild itching for 12 weeks after the end of therapy, all adverse events resolved by the time the participants were due to check SVR-12. Figure 2 depicts the frequencies of each reported adverse event and their changes over time.

Lastly, the HQLQ scores showed marked improvements in all domains over time. Between their baseline evaluations and their visits while on treatment, patients showed a statistically significant decrease in the self-evaluated health transition (SET) item scores (P <.001). Moreover, scores of the mental health component (MCS), general health distress (HD), psychological well-being (PWB), hepatitis-specific functional limitations (HLIM), and hepatitis-specific health distress (HHD) increased significantly (P ≤0.01), which indicates lower levels of psychological distress, fewer limitations in social activities due to emotional problems, less general and

| Characteristics | Baseline | On treatment | SVR-4 timepoint | SVR-12 timepoint |
|-----------------|----------|-------------|----------------|-----------------|
| Transient elastography | 6.02±1.42 kPa | - | - | - |
| Viral load | 3,498,328±1,583,778 IU/mL (26-20,771,869) | <15-60 IU/mL | <15-2,822 IU/mL | <15-1,680,070 IU/mL |
| Alanine aminotransferase (ALT) | 59±64 U/L (8-236) | 17±9.6 U/L (7-52) | 15±8.5 U/L (6-50) | 16±8.6 U/L (8-45) |
| Aspartate aminotransferase (AST) | 47±55 U/L (12-297) | 21±9.1 U/L (12-62) | 18.5±5.3 U/L (13-37) | 19±5.6 U/L (14-40) |
| Alkaline phosphatase (ALP) | 93±41 U/L (51-271) | 90±21 U/L (48-127) | 81.5±19 U/L (45-135) | 81±19.4 U/L (45-127) |
| Alpha-fetoprotein (AFP) | 4.59±3.52 ng/mL (2-15) | - | - | 2.9±0.89 ng/mL (2-4.9) |
| Bilirubin (Total) | 12±2 µmol/L (3-98) | 13±13 µmol/L (4-8.71) | 11.2±14 µmol/L (2.2-81) | 7.6±3.9 µmol/L (2.6-21.7) |
| Bilirubin (Direct) | 6.1±12 µmol/L (1.8-67) | 4.5±3.8 µmol/L (1.8-23) | 3.6±1.9 µmol/L (1.8-12) | 3.2±1.6 µmol/L (1.8-9.7) |
| Sodium | 138±2 mEq/L (132-142) | 139±1.6 mEq/L (136-142) | 139±1.7 mEq/L (134-142) | 138±1.3 mEq/L (135-140) |
| Potassium | 3.84±0.34 mmol/L (3.1-4.68) | 3.9±0.36 mmol/L (3.27-4.61) | 4±0.34 mmol/L (3.1-4.6) | 3.93±0.39 mmol/L (3.1-4.6) |
| Creatinine | 62±13 µmol/L (46-95) | 66±4.13 µmol/L (44-91) | 65±14 µmol/L (46-102) | 64±11.4 µmol/L (44-90) |

†Values are expressed as mean±SD (minimum - maximum value) and ‡represent sustained virologic response at 4 and 12 weeks after the end of treatment, respectively.
hepatitis-related health distress, and higher levels of overall well-being compared to baseline. Between the second and third time points (i.e., on treatment and after the end of treatment, respectively), changes in MCS, HD, PWB, and HHD scores remained significant \((P \leq 0.048)\). Changes in the HLIM and SET item scores between the second and third time points, however, did not \((P \geq 0.059)\).

The most remarkable quality of life changes occurred between the first (baseline) and third (12 weeks after treatment) time points. Differences between these two points were significant and included the mental, hepatitis-specific, and self-evaluated health transition items \((P <.0001)\). Furthermore, the increase in the physical health component (PCS) scores was only significant between these two time points \((P =0.001)\). Higher PCS scores indicate little physical limitations/disabilities, high energy levels, and good general health. Changes in the average HQLQ scores over the three time points are shown in Figure 3.

**DISCUSSION**

ELEGANT-4 was an open-label, single-arm trial conducted at a tertiary care centre in Riyadh, Saudi Arabia. Thirty patients were treated with a shortened, 8-week course of ELB/GZR, of whom 29 (97%) achieved SVR-4 and SVR-12. Achieving SVR is an HCV cure marker that has been shown to be durable on the long term. Data from large, prospective cohort studies with ≥5 years of follow-up show that SVR is a lasting indicator of HCV eradication in >99% of patients.\[11\] Additionally, there were no serious adverse events associated with the course of treatment used in our study, and significant improvements were found in all parameters that were used to evaluate the patients’ quality of life.

Achieving complete viral cure from HCV can be affected by many factors other than medication efficacy. In essence, one of the key determinants of treatment success on an individual level is patient compliance.\[8\] In the context of HCV treatment, cost, adverse events, and long treatment duration can be significant barriers. The use of regimens with shorter durations can minimize the cost and side-effects, and thereby enhance adherence.

The combination of Elbasvir/Grazoprevir is generally used for 12 weeks in treatment naive individuals, and has an efficacy of 96% against genotype 4, whether or not given with ribavirin.\[12\] Nonetheless, an 8-week course of Elbasvir/Grazoprevir has been evaluated with other HCV genotypes. For instance, the C-SWIFT trial combined Elbasvir/Grazoprevir with Sofosbuvir and used variable treatment durations (4–12 weeks) in patients infected with HCV genotypes 1 and 3. The 8-week regimen yielded 81% SVR-12 rate in cirrhotic patients with genotype 1 and 93% rate in non-cirrhotic patients with genotype 3.\[13\] Lower response rates were found in the C-WORTHY and C-CREST trials. The C-WORTHY study used ELB/GZR with no concomitant DAAs, and found 80% SVR-12 rates among patients who were mono-infected with genotype 1a.\[14\] Fortunately, studies on genotypes 1b and 4 patients show more promising results. In the EGALITE study, for example, SVR-12 rates ranged between 90 and 100% in genotype 1b patients (per protocol analysis).\[15\]
Similarly, a recent randomized trial on genotype 4 patients reported 94 and 96% success with 8- and 12-week ELB/GZR regimens, respectively.\[16\] One of the main strengths of the aforementioned study was the enrollment of a relatively large group of ethnically and genotypically diverse patients (different genotype 4 subtypes). Like our trial, however, it was not designed to evaluate the non-inferiority of an 8-week ELB/GZR regimen to a 12-week one. With the limited evidence that exists on shorter treatment durations in genotype 4-infected individuals, there is only one 8-week regimen that is currently approved for this patient population; a daily combination of Glecaprevir/Pibrentasvir. An 8-week-regimen of Ledipasvir/Sofosbuvir can also be considered, but only in patients with favorable baseline characteristics (no cirrhosis, viral load <6 million IU/mL, and absence of genotype 4r).\[17,18\] Therefore, future powered, non-inferiority trials are warranted to explore more treatment options in this group.

One patient failed to sustain the reduction of viral load after having an undetectable HCV RNA in our study. Historically, response to interferon-based HCV treatment included patient and viral predictors. Patient-related factors that were associated with better outcomes included female gender, younger age, normal body mass index (BMI), absence of advanced liver fibrosis, having no history of failed treatment, and interleukin 28B (IL28B) CC genotype. Conversely, co-morbid conditions such as coinfection with HIV, insulin resistance, or diabetes, used to be associated with undesirable outcomes.\[19-21\] That said, little evidence exists on the predictors of response to DAAs. In a 2019 retrospective cohort analysis, the authors suggested that ongoing drug use and mental illness were significant predictive variables in HIV co-infected patients.\[22\] However, none of these factors were present with our patient. Another 2019 study suggested a role of viral load (≥1,500,000 IU/mL) and having >15% frequency of baseline Y93H resistance-associated substitution (RAS), a substitution usually associated with genotypes 1b and 3.\[15,23\] Moreover, the current recommendations of the European Association for the Study of Liver (EASL) go against using a 12-week ELB/GZR course to treat genotype 4 patients with HCV RNA levels ≥800,000 IU/mL.\[16,18\] While most of our patients (57%) had baseline HCV RNA levels remarkably higher than 800,000 IU/mL, it is possible that having a high baseline viral load (>4,000,000 IU/mL) may have contributed to this patient’s inability to sustain virologic response.

As mentioned above, minimizing the occurrence of adverse events is one of the main expected advantages of shortening the treatment duration. In this trial, 53% of patients experienced adverse events while on treatment, 94% of which resolved by the time the patients achieved SVR-12. Further, none of the reported side-effects was serious or life-threatening, and none led to treatment discontinuation. The latter goes in line with the findings of a recent trial that randomized 117 genotype 4 patients to 8- and 12-week ELB/GZR arms.\[16\] While it is difficult to draw conclusions about the role of using a shorter ELB/GZR course on adverse events from our study, the use of a standard-care control arm provides useful information in that context. In the aforementioned randomized trial, there were fewer adverse events associated with the shorter treatment arm.

Large and significant improvements in quality of life parameters between baseline and SVR-12 were observed in this trial. In previous studies, small but significant positive changes in certain quality of life aspects were associated with viral eradication with other DAAs.\[24,25\] In analyses of the pooled patients from the ION-1, 2 and 3 trials, viral eradication during Ledipasvir/Sofosbuvir treatment was associated with significant physical and mental improvements in the standard SF-36 v2 health survey, that is usually used to assess health-related quality of life.

**Figure 3:** Changes in the HQLQ scores over the study period. Chart (a) represents the scores of the physical and mental components, as well as the self-evaluated transition (SET) item. Higher scores on the physical and mental components reflect more favorable results. The opposite is true for the SET. SET scores are multiplied by 10 to showcase the trend clearly. Chart (b) showcases the overall trends for hepatitis-specific items. Higher scores on these indices represent more favorable outcomes.
of life (HRQoL). Mean changes in scores ranged between 2 and 7 points out of a possible 100.\[23]\] In this trial, average score changes ranged from 6 to 19 points (out of a possible 100) for the physical and mental components, respectively, and from 18 to 45 points for hepatitis-specific items. While large changes in general health with a 12-week course of ELB/GZR have been documented in previous reports,\[26,27]\] to our knowledge, this was the first study to evaluate the effects of a shorter treatment duration using hepatitis-specific indices.

In conclusion, ELEGANT-4 provides empirical evidence that HCV genotype 4-infected individuals can be successfully treated with an 8-week regimen of ELB/GZR regardless of baseline viral load. Further, there were no serious adverse events associated with this course of treatment, and significant improvements can emerge in terms of general and hepatitis-specific health-related quality of life. The findings of this study emphasize the importance of screening and early HCV detection, not only because of all-cause and liver-related mortality and morbidity benefits, but also because shorter, more affordable treatment courses can be used if the infection is found early.\[21]\] Nevertheless, data from high-quality, statistically powered, randomized non-inferiority trials are needed to establish solid conclusions about how an 8-week course of ELB/GZR compares to a 12-week course, in terms of efficacy, patient adherence, and health-related quality of life.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. World Health Organization. World Health Statistics Overview 2019: Monitoring Health for the SDGs, Sustainable Development Goals. Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/handle/10665/324835. License: CC BY-NC-SA 3.0 IGO.
2. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71.
3. Blach S, Zeuzem S, Manns M, Altraif I, Duberg A, Mjuljono DH, \textit{et al.} Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. Lancet Gastroenterol Hepatol 2017;2:161-76.
4. World Health Organization. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/. License CC BY-NC-SA 3.0 IGO.
5. Asselah T, Marcellin P, Schinzari RF. Treatment of hepatitis C virus infection with direct-acting antiviral agents: 100% cure? Liver Int 2018;38(Suppl 1):7-13.
6. Liang TJ, Rehermann B, Sceff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med 2000;132:296-305.
7. Tan S. Hepatitis C Viruses: Genomes and Molecular Biology. Norfolk (UK): Horizon Bioscience; 2006.
8. Tan S. HCV NSSA: A multifunctional regulator of cellular pathways and virus replication. In: He Y, Staschke K, Tan S-L, editors. Hepatitis C Viruses: Genomes and Molecular Biology. Norfolk, UK: Horizon Bioscience; 2006.
9. Arief I, Bonnet D. Grazoprevir+elbasvir for the treatment of hepatitis C virus infection. Expert Opin Pharmacother 2016;17:735-42.
10. Bayliss MS, Maruish ME, editors. Hepatitis Quality of Life QuestionnaireTM, v2: [HQLQv2TM] Administration and Scoring Supplement. Lincoln, NE: QualityMetric Incorporated; 2004.
11. When and in Whom to Initiate HCV Therapy | HCV Guidance [Internet]. Hcvguidelines.org. 2020. Available from: https://www.hcvguidelines.org/evaluate/when-whom [-last accessed on 2019 Nov 06].
12. Asselah T, Reesink H, Gerstoft J, de Ledinghen V, Pockros PJ, Robertson M, \textit{et al.} Efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype 4 infection: A pooled analysis. Liver Int 2018;38:1583-91.
13. Lawrie E, Poordad F, Gutierrez JA, Wells JT, Landaverde CE, Evans B, \textit{et al.} Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. Hepatology 2017;65:439-50.
14. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, \textit{et al.} Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HCV/hepatitis C virus co-infection (C-WORTHY): A randomised, open-label phase 2 trial. Lancet 2015;385:1087-97.
15. Huang C, Hung C, Cheng P, Bair M, Huang Y, Kao J, \textit{et al.} An open-label, randomized, active-controlled trial of 8 versus 12 weeks of elbasvir/grazoprevir for treatment-naive patients with chronic hepatitis C genotype 1b infection and mild fibrosis (EGALITE study): Impact of baseline viral load and NSSA resistance-associated substitutions. J Infect Dis 2019;220:557-66.
16. Asselah T, Pol S, Hezode C, Loustaud-Ratti V, Leroy V, Ahmed SN, \textit{et al.} Efficacy and safety of elbasvir/grazoprevir for 8 or 12 weeks for hepatitis C virus genotype 4 infection: A randomized study. Liver Int 2020;40:1042-51.
17. Treatment Naïve Genotype 4 Without Cirrhosis | HCV Guidance [Internet]. Hcvguidelines.org. 2020. Available from: https://www.hcvguidelines.org/treatment-naive/gt4/no-cirrhosis. [Last accessed on 2021 Sep 29].
18. Pawlotsky J, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, \textit{et al.} EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
19. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3:47-52.
20. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61 (1 Suppl):S58-66.
21. Matsuura K, Watanabe T, Tanaka Y. Role of IL28B for chronic hepatitis C treatment toward personalized medicine. J Gastroenterol Hepatol 2014;29:241-9.
22. Cachay ER, Mena A, Morano I, Benitez I, Maidla I, Ballard C, \textit{et al.} Predictors of hepatitis C treatment failure after using direct-acting antivirals in people living with human immunodeficiency virus. Open Forum Infect Dis 2019;6:coz070.
23. Wyles DL, Luethke Mayer AF. Understanding hepatitis C virus drug resistance: Clinical implications for current and future regimens. Top
24. Younossi ZM, Stepanova M, Feld J, Zeuzem S, Jacobson I, Agarwal K, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: Results from ASTRAL-1 placebo-controlled trial. J Hepatol 2016;65:33-9.

25. Bruchfeld A, Roth D, Martin P, Nelson DR, Pol S, Londoño M, et al. Elbasvir plus grazoprevir in patients with hepatitis C virus infection and stage 4–5 chronic kidney disease: Clinical, virological, and health-related quality-of-life outcomes from a phase 3, multicentre, randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol 2017;2:585-94.

26. Cheng W, Sobhonslidsuk A, Thu Pham TT, Wang FS, Lee YJ, Chu CJ, et al. Impact of a 12-week oral regimen of elbasvir/grazoprevir (EBR/GZR) on health-related quality of life (HRQOL) and fatigue in treatment-naïve patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, or 6 infection: Data from the C-CORAL study. In: 26th Conference of the Asian Pacific Association for the Study of the Liver. Shanghai, China: Conference Reports for NATAP; 2017.

27. Ng X, Nwankwo C, Arduino JM, Corman S, Lasch KE, Lauhrino JM, et al. Patient-reported outcomes in individuals with hepatitis C virus infection treated with elbasvir/grazoprevir. Patient Prefer Adherence 2018;12:2631-8.