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Clinically Meaningful Differences in Health-Related Quality of Life and Fatigue in Patients With Hepatitis C Virus (HCV) Infection Treated With Elbasvir/Grazoprevir (EBR/GZR) Compared to Sofosbuvir (SOF) With Pegylated Interferon and Ribavirin (PR)

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Introduction

- Hepatitis C virus (HCV) leads to decreased health-related quality of life (HRQoL) and increased fatigue in patients with chronic HCV, even in the absence of advanced liver disease[1-3]
- HRQoL can improve in chronic HCV patients who respond to treatment, but on-treatment HRQoL may vary based on the tolerability profile of the treatment regimens used
- This potential variation in on-treatment HRQoL between regimens can be assessed using data from randomized clinical trials
- However, the clinical meaningfulness of often-reported change scores in HRQoL between regimens is sometimes not intuitively apparent
- C-EDGE H2H was a randomized, open-label multinational trial that compared the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) versus sofosbuvir with pegylated interferon and ribavirin (SOF/PR) in patients with genotype 1, 4, or 6 chronic HCV infection[6]
- The study sample consisted of 255 patients, with the majority of patients having HCV GT1b infection (82.0%) and being treatment-naïve (74.9%) and non-cirrhotic (83.1%).[6] Patients were randomized to one of two treatment regimens:
  - Sofosbuvir 400 mg once daily + PegIntron® 1.5 mcg/kg once weekly + weight-based ribavirin 1000-1200 mg/day for 12 weeks
  - Elbasvir 50 mg / grazoprevir 100 mg once daily for 12 weeks
- The primary efficacy objective was sustained virologic response 12 weeks after the end of therapy (SVR12, HCV RNA <15 IU/mL). EBR/GZR was observed to have superior efficacy, safety, and tolerability in patients with HCV GT1 or 4 infection compared with SOF/PR, with SVR12 rates of 99.2% (128/129) and 90.5% (114/126) in the EBR/GZR and SOF/PR groups, respectively[6]
- As part of the study, data on HRQoL and fatigue were also collected using the SF-36v2® Health Survey Acute (1-week recall) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale

Aim

- Therefore, the aims of the current study were to:
  - Describe and compare the impact of EBR/GZR versus SOF/PR on changes in HRQoL and fatigue during and after treatment
  - Assess whether any observed differences in HRQOL and fatigue between the two treatment groups are clinically meaningful

Methods

Data sources

- 247 study patients from the C-EDGE H2H study had a baseline and ≥1 follow-up assessment on the SF-36v2 and FACIT-Fatigue and so were included in the analysis
- SF-36v2® Health Survey Acute (1-week recall)
  - Consists of 36 items, used to create 8 health domains that are transformed onto 0 – 100 scale. Higher scores indicate better health status
    - Physical functioning
    - Role limitations due to physical health
    - Role limitations due to emotional problems
    - Vitality
    - Social functioning
    - Mental health
    - Bodily pain
    - General health
  - Scores are summarized into 2 overall scores, the Physical and Mental Component Summary scores (PCS and MCS), which are calibrated such that a score of 50 represents a US population norm
- FACIT-Fatigue Scale
  - Consists of 13 items, used to create a total Fatigue score of 0 – 52, where a higher score indicates better functioning

Analysis

- Analyses were conducted using the patient-reported outcome full analysis set (PRO FAS), which consisted of all enrolled patients who had at least one dose of study medication and had completed at least one baseline or post-baseline PRO assessment
- Change from baseline at weeks 4 and 12 on treatment and follow-up week 12 were assessed
  - Mean change from baseline scores was calculated by treatment group
  - The difference in mean change from baseline scores (EBR/GZR - SOF/PR) with 95% confidence intervals was estimated
  - Effect sizes were calculated as the mean difference divided by the standard deviation of the difference scores
- The literature was reviewed for established minimal clinically important differences (MCID) for the SF-36v2® and FACIT-Fatigue Scale
  - MCID can be defined as "the smallest difference which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management"[7]
  - An MCID was available for the Vitality domain of the SF-36v2® in the study population, where a change of >4.2 has been proposed[8]
  - No MCIDs were available for the remaining domains or component score of the SF-36v2® or the FACIT-Fatigue for this patient population
  - Therefore, the difference between treatment means for change from baseline was converted to effect sizes (ES) and compared to standardized criteria based on Cohen,[9] where: <0.2 = small effect, 0.5 = moderate effect, and >0.8 = large effect

Results

Overall

- There was a decrease in HRQoL from baseline to week 4 in both groups during treatment, with patients in the SOF/PR treatment arm showing a higher decrement in HRQoL (**Figure 1** and **2**)
- This trend of a reduction in HRQoL was also observed at week 12 of treatment forthe SOF/PR treatment arm, while for patients in the EBR/GZR treatment arm, a trend of improvement in HRQoL was observed (**Figure 1** and **2**)
- At follow-up week 12, the observed improvement in HRQoL at week 12 was maintained in patients in the EBR/GZR treatment arm. HRQoL for patients in the SOF/PR treatment arm returned close to baseline except for in general health and role limitations – physical, where improvements were observed (**Figure 1** and **2**)
- A similar trend was observed for fatigue (data not shown)

Figure 1. EBR/GZR treatment arm: change from baseline for SF-36v2® (PRO FAS)

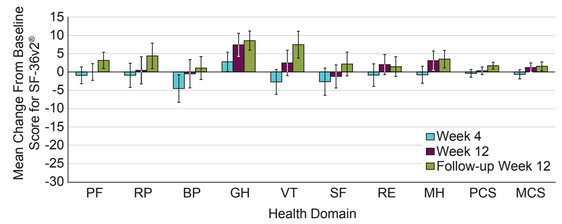
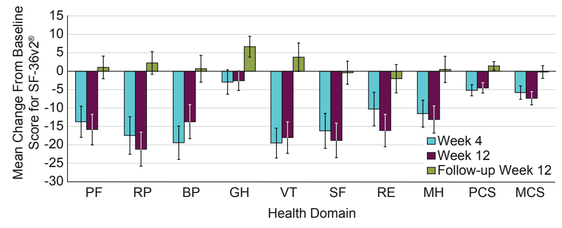


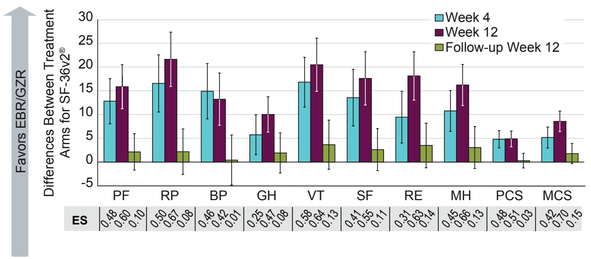
Figure 2. SOF/PR treatment arm: change from baseline for SF-36v2® (PRO FAS)



SF-36v2® Health Survey

- Baseline mean scores were similar between treatment arms
- During treatment, the ES for the difference between treatment arms on the 8 domains of the SF-36v2® and the PCS and MCS ranged from 0.25 (general health) to 0.58 (Vitality) at week 4 and 0.42 (bodily pain) to 0.70 (MCS) at week 12 (**Figure 3**)
- These differences between the arms represent a clinically meaningful impact on HRQoL favoring EBR/GZR, reflecting a moderate ES (**Figure 3**)
- After the completion of treatment, ES ranged from 0.01 (bodily pain) to 0.15 (MCS), reflecting a small effect
- The results reflected overall improvement in comparison with baseline HRQoL for both groups at follow-up, with no clinically meaningful difference between the arms
- MCID for Vitality Domain
  - Difference in mean change from baseline between groups for Vitality exceeded the MCID >4.2 during treatment only. After treatment the difference was <4.2

Figure 3. Summary of differences between treatment arms and effect sizes for change from baseline for SF-36v2® by domain (PRO FAS)



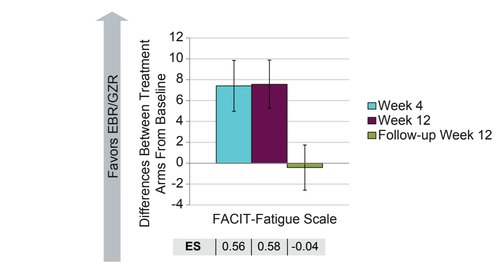
Effect sizes (ES): <0.2 = small effect, 0.5 = moderate effect, and >0.8 = large effect.

Abbreviations: BP, Bodily pain; GH, General health; MCS, Mental Component Summary; MH, Mental health; PCS, Physical Component Summary; PF, Physical functioning; RE, Role limitations-emotional; RP, Role limitations-physical; VT, Vitality; SF, Social functioning.

FACIT-Fatigue Scale

- Baseline mean scores were similar between treatment arms
- During treatment, the ES for the difference between treatment arms was 0.56 at week 4, 0.58 at week 12 (**Figure 4**)
- These differences between the arms represent a clinically meaningful impact on Fatigue, favoring EBR/GZR, reflecting a moderate ES (**Figure 4**)
- After the completion of treatment, the ES was -0.04, reflecting a small effect that was not considered to be clinically meaningful

Figure 4. Summary of differences between treatment arms and effect sizes for change from baseline in FACIT-Fatigue scale (PRO FAS)



Effect sizes (ES): <0.2 = small effect, 0.5 = moderate effect, and >0.8 = large effect.

Conclusions

In the C-EDGE H2H study:

- Overall, a trend of an improvement in HRQoL and fatigue was observed in patients in the EBR/GZR treatment arm at week 12 and follow-up week 12, whereas a trend of decrease in HRQoL and fatigue was observed at week 12 in the SOF/PR treatment arm
- HRQoL was statistically significantly better for patients treated with EBR/GZR as compared to SOF/PR, as measured by all 8 SF-36v2® domains and Physical and Mental Component Summary scores as well as FACIT-Fatigue scale at weeks 4 and 12 of treatment
  - These scale differences were also clinically meaningful, as measured by moderate effect sizes for SF-36v2® physical functioning, role limitations-physical, vitality, social functioning, role limitations-emotional, and mental health domains as well as Physical and Mental Component Summary scores
  - FACIT-Fatigue scores also significantly differed at weeks 4 and 12, with no significant differences between groups at follow-up week 12. Effect sizes were moderate at weeks 4 and 12
  - One reason for this observed difference during treatment may be attributable to the difference in the tolerability profile of the two regimens, with EBR/GZR demonstrating superior safety and tolerability relative to SOF/PR in the study
- Clinically meaningful differences between groups were not present by the 12-week follow-up visit on all measures
  - However, for EBR/GZR patients, there still were significantly improved SF-36v2® physical functioning, role limitations-physical, general health, vitality, mental health, and PCS and MCS scores from baseline at the 12-week follow-up (data not shown), indicating that some improvement from baseline was retained
- Study limitations
  - This was an open-label trial, and it is unknown how much of an impact knowing the treatment assignment had on the results

References

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