Successful Treatment of Cirrhotic People With HCV GT3 Infection With Elbasvir/Grazoprevir Plus Sofosbuvir ± Ribavirin Does Not Correct Insulin Resistance

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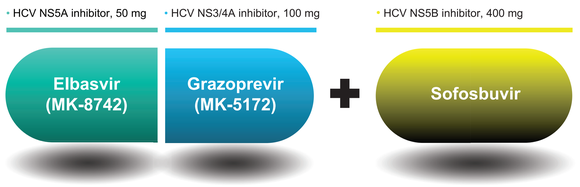
Foster GR[1]; Agarwal K[2]; Cramp M[3]; Moreea S[4]; Barclay S[5]; Collier J[6]; Brown AS[7]; Ryder SD[8]; Ustianowski A[9]; Forton DM[10]; Fox R[11]; Gordon F[12]; Rosenberg WM[13]; Mutimer DJ[14]; Du J[15]; Gilbert CL[15]; Robertson MN[15]; Barr E[15]; Haber B[15]

[1]The Royal London Hospital, London, UK; [2]Institute of Liver Studies, Kings College Hospital, London, UK; [3]South West Liver Unit, Derriford Hospital and Peninsula School of Medicine and Dentistry, Plymouth, UK; [4]Bradford Teaching Hospitals Foundation Trust, Bradford, UK; [5]Glasgow Royal Campus, Glasgow, UK; [6]John Radcliffe Hospital, Oxford, UK; [7]Imperial College Healthcare, London, UK; [8]NIHR Biomedical Unit in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and The University of Nottingham, Nottingham, UK; [9]North Manchester General Hospital, Manchester, UK; [10]St. Georges University of London, London, UK; [11]Gartnavel General Hospital, Glasgow, UK; [12]Hepatology Joint Clinical Research Unit, Bristol, UK; [13]University College London, London, UK; [14]QE Hospital, Birmingham, UK; [15]Merck & Co., Inc., Kenilworth, NJ, USA

Background

- Insulin resistance and altered lipoprotein metabolism are features of hepatitis C virus (HCV) genotype (GT)3 infection
  - Advanced cirrhosis is associated with insulin insensitivity and reduced glucose effectiveness[1]
  - In individuals with HCV GT1 or 3 infection, insulin resistance is correlated with degree of fibrosis[2,3]
    - People with more advanced fibrosis have a higher degree of insulin resistance[2,3]
  - HCV viral clearance is associated with improved insulin resistance in individuals with some genotypes[4]
    - People with GT1 infection showed improved insulin resistance, but not those with HCV GT2/3 infection[4]
    - However, most people with GT3 infection in this study had mild liver fibrosis (METAVIR F0-F1), and only 29% had insulin resistance[4]
- Studies have shown insulin resistance to be negatively associated with sustained virologic response (SVR) in people with HCV infection, including those with GT3 infection, receiving peginterferon/ribavirin (PR) therapy[5,6]
- We therefore hypothesized that:
  - Successful treatment of HCV GT3 infection may improve insulin resistance
  - Virologic failure may be increased in people with insulin resistance
- Elbasvir (EBR) is a once-daily NS5A inhibitor and grazoprevir (GZR) is a once-daily HCV NS3/4A protease inhibitor (**Figure 1**)
  - The combination of EBR and GZR is approved in Europe, the United States, Canada, and other countries worldwide[7]
  - Broad activity vs most HCV genotypes in vitro[8-10]
  - Efficacious in treatment-naive and -experienced individuals, cirrhotic and noncirrhotic individuals, HIV/HCV co-infected individuals, and those with chronic kidney disease[11-14]
- Sofosbuvir (SOF) is an NS5B inhibitor indicated for the treatment of chronic HCV infection as a component of a combination antiviral treatment regimen[15]

Figure 1. EBR/GZR plus SOF



Aim

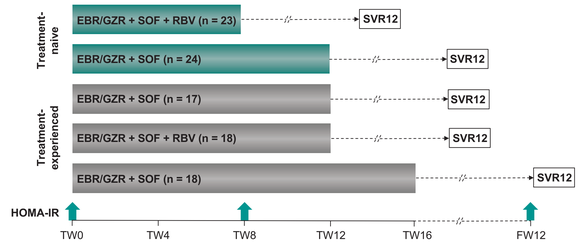
- To assess the effect of HCV therapy on insulin resistance and its relationship with treatment outcome in people with HCV GT3 infection and cirrhosis receiving EBR/GZR plus SOF ± ribavirin (RBV)

Participants and Methods

Study Design

- C-ISLE (NCT02601573; Protocol PN083-02) was a randomized, open-label, UK-based clinical trial in HCV GT3-infected participants with compensated cirrhosis (**Figure 2**)
- Adult participants with chronic HCV GT3 infection were included
  - Compensated liver cirrhosis defined by liver biopsy (METAVIR F4) or transient elastography (>12.5 kPa)
  - Treatment-naive, experienced to PR, monoinfected or HIV co-infected
- All participants received EBR 50 mg/GZR 100 mg plus SOF (400 mg as per prescribing information) ± RBV 800-1400 mg/day
  - Treatment-naive participants were treated for 8 or 12 weeks
  - Treatment-experienced participants were treated for 12 or 16 weeks
    - Randomization of treatment-experienced participants was stratified based on prior relapse vs nonrelapse (partial, null, interferon-intolerant)
  - Target enrollment was 25 participants per arm
  - The primary endpoint was SVR 12 weeks after completion of therapy (SVR12, HCV RNA <15 IU/mL [cobas® TaqMan® v2.0])

Figure 2. Study design



FW, follow-up week; HOMA-IR, homeostatic model assessment of insulin resistance; TW, treatment week.

- Change in insulin resistance during treatment and follow-up was assessed as an exploratory outcome
  - Homeostatic model assessment of insulin resistance (HOMA-IR) is a surrogate assessment of insulin resistance
    - HOMA IR = [insulin (μIU/mL) × glucose (mg/dL)]/405
  - Assessments of insulin resistance were measured using HOMA-IR at baseline, treatment week (TW)8, and follow-up week (FW)12
  - Normative HOMA-IR values of (mean ± standard deviation) 2.0 ± 1.1 in people without diabetes and 1.9 ± 1.1 in people with diabetes were derived from a previous study[16]
  - A conservative threshold of HOMA-IR ≥3.0 was employed to define insulin resistance, as used in previous studies of people with HCV infection[4,17]

Results

Demographics and Characteristics

- 100 participants with HCV GT3 infection and compensated cirrhosis were enrolled (**Table 1**)

Table 1. Demographics

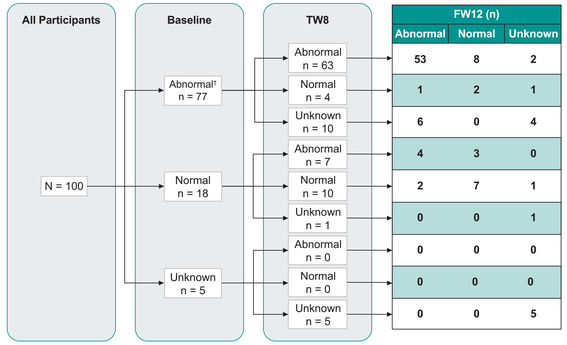
	Cirrhotic GT3-infected participants (n = 100)
Male, n (%)	68 (68)
Race, n (%) Asian White Other	 29 (29) 69 (69) 2 (2)
Age, years, mean (SD)	53.4 (8.7)
Cirrhosis diagnosis method Liver biopsy, n (%) FibroScan®, n (%) FibroScan® score, kPa, mean (SD)	 16 (16) 84 (84) 25.4 (12.1)
Prior treatment history, n (%) Naive PR-experienced	 47 (47) 53 (53)
HCV RNA $\log_{10}$, IU/mL, mean (SD)	6.2 (0.7)
IL28B CC, n (%)	50 (50)
Albumin, g/dL, mean (SD)	3.6 (1.2)
ALT IU/L, median (range)	94 (21-389)
Total bilirubin, mg/dL, mean (SD)	0.7 (0.4)
Platelets × 10^3 cells/μL, median (range)	138 (46-396)
Platelet count <100 × 10^3 cells/μL, n (%)	24 (24)
BMI ≥30 kg/m^2, n (%)	28 (28)
History of diabetes, n (%)	23 (23)
Glucose, mg/dL, median (range)	97 (53-409)
Insulin, μIU/mL Median (range) Mean (SD)	 21.0 (2.8-495.5) 40.78 (63.39)
HOMA-IR Median (range) Mean (SD)	 5.57 (0.48-209.21) 14.06 (26.49)

ALT, alanine aminotransferase; BMI, body mass index; SD, standard deviation.

Change in HOMA-IR Values During Treatment and Follow-Up

- 81% (77/95), 83% (70/84), and 77% (66/86) of participants had HOMA-IR ≥3.0 at baseline, TW8, and FW12, respectively (**Figure 3**)
- 86% of participants with HOMA-IR ≥3.0 at baseline continued to have elevated HOMA-IR at FW12

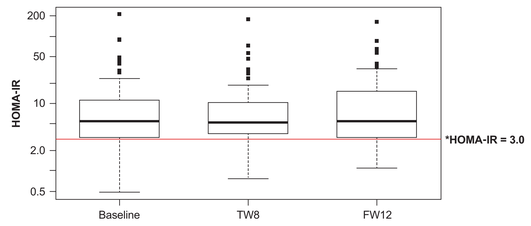
Figure 3. Change in HOMA-IR values during treatment and follow-up



†Abnormal is defined as HOMA-IR ≥3.0.

- There was no apparent change in median HOMA-IR values during treatment or follow-up (**Figure 4**)

Figure 4. Median HOMA-IR values during treatment and follow-up



HOMA-IR, median (range)			
	5.57 (0.48-209.21)	5.27 (0.75-173.84)	5.52 (1.10-163.83)

Box and whisker plots represent median values (heavy horizontal line), 25th and 75th percentiles (box), and the lowest/highest data points within 1.5 interquartile range of the 25th/75th quartile (whiskers). Data outside of these parameters is shown as outliers (filled square symbols).
*HOMA-IR values >3.0 (red line) were considered as insulin-resistant.

Virologic Failures

- Two participants receiving EBR/GZR + SOF for 8 weeks experienced virologic failure
  - There were no virologic failures among the participants receiving EBR/GZR for 12 weeks
- At baseline, both participants who relapsed had HOMA-IR values below median for the overall study population (**Table 2**)
  - Neither participant who relapsed had a history of diabetes. This indicates that insulin control at baseline was better in these 2 participants compared with the overall study population
  - One participant who relapsed had decreased HOMA-IR following therapy. This observation is of unclear significance

Table 2. Change in HOMA-IR values in participants who relapsed

HOMA-IR values	Baseline	TW8	FW12
Relapse patient 1	5.11	4.85	2.13
Relapse patient 2	3.91	5.34	3.90
Overall median	5.57 (0.48-209.21)	5.27 (0.75-173.84)	5.52 (1.10-163.83)

Conclusions

- In the present study, participants with HCV GT3 infection and cirrhosis were notable for a high incidence of diabetes
  - 23% of participants had a medical history of diabetes
  - 81% of participants had HOMA-IR ≥3.0 at baseline
- Median HOMA-IR values did not improve for these participants during or following therapy
- These data do not support an association between insulin resistance and virologic failure
  - The small number of participants with virologic failure makes interpretation of these data difficult
  - Insulin resistance as a predictor of SVR may be of limited relevance in the era of highly effective DAA therapies

References

1. Kruszynska YT, Harry DS, Bergman RN, McIntyre N. Insulin sensitivity, insulin secretion and glucose effectiveness in diabetic and non-diabetic cirrhotic patients. *Diabetologia.* 1993;36:121-128.
2. Bugianesi E, Marchesini G, Gentilcore E, et al. Fibrosis in genotype 3 chronic hepatitis C and nonalcoholic fatty liver disease: role of insulin resistance and hepatic steatosis. *Hepatology.* 2006;44:1648-1655.
3. Cua IHY, Hui JM, Kench JG, George J. Genotype-specific interactions of insulin resistance, steatosis, and fibrosis in chronic hepatitis C. *Hepatology.* 2008;48:723-731.
4. Thompson AJ, Patel K, Chuang W-L, et al; for the ACHIEVE-1 and ACHIEVE-2/3 Study Teams. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. *Gut.* 2012;61:128-134.
5. Conjeevaram HS, Kleiner DE, Everhart JE, et al; for the Virahep-C Study Group. Race, insulin resistance and hepatic steatosis in chronic hepatitis C. *Hepatology.* 2007;45:80-87.
6. D'Souza R, Sabin CA, Foster GR. Insulin resistance plays a significant role in liver fibrosis in chronic hepatitis C and in the response to antiviral therapy. *Am J Gastroenterol.* 2005;100:1509-1515.
7. Zepatier [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2016.
8. Summa V, Ludmerer SW, McCauley JA, et al. MK-5172, a selective inhibitor of hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants. *Antimicrob Agents Chemother.* 2012;56:4161-4167.
9. Harper S, McCauley JA, Rudd MT, et al. Discovery of MK-5172, a macrocyclic hepatitis C virus NS3/4a protease inhibitor. *ACS Med Chem Lett.* 2012;3:332-336.
10. Coburn CA, Meinke PT, Chang W, et al. Discovery of MK-8742: an HCV NS5A inhibitor with broad genotype activity. *ChemMedChem.* 2013;8:1930-1940.
11. Kwo P, Gane E, Peng C-Y, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. *Gastroenterology.* 2017;152:164-175.e4.
12. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet.* 2015;386:1537-1545.
13. Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV.* 2015;2:e319-e327.
14. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med.* 2015;163:1-13.
15. Sofosbuvir [package insert]. Foster City, CA: Gilead Sciences; 2017.
16. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord.* 2013;13:47.
17. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology.* 2008;134:416-423.

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