Incidence of Hepatocellular Carcinoma Among Patients With Hepatitis C Virus Infection Following Treatment With a Grazoprevir-Containing Regimen

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INTRODUCTION

- The incidence of hepatocellular carcinoma (HCC) in the United States increased between 2000 and 2012, predominantly as a result of the aging of the HCV-infected population[1]
- There has also been a progressive increase in the global number of people with primary liver cancer (mostly HCC), from 437,408 to 714,600 between 1990 and 2002[2,3]
- The reported annual incidence of HCC among individuals with hepatitis C virus (HCV) infection ranges from 1% to 3%[4]
- Although controversial, it has been hypothesized that initiation of direct-acting antiviral (DAA) therapy for the treatment of HCV infection may result in de novo or recurrent HCC[5,6]
- Thus, understanding the risk of HCC associated with initiation of DAA therapy is important for assessing the risk-benefit ratio of treatment decisions for HCV therapy
- The incidence of HCC following treatment with a grazoprevir (GZR)–containing regimen has not been previously reported

AIM

- To describe the incidence of HCC following therapy with a GZR-containing regimen and the characteristics of those participants who developed HCC

METHODS

- Extraction of data from a long-term extension study of individuals with HCV infection who participated in clinical trial studies with observational follow-up for a maximum of 5 years
  - Participants who had received a GZR-containing regimen in the phase 2 and 3 clinical trials of the GZR clinical development program were enrolled following the clinical trial follow-up week 24 visit
  - Clinic visits occurred at baseline and every 6 months thereafter for a total duration of up to 5 years
    - Clinic visits included physical examination, measurement of HCV RNA, complete blood count, and comprehensive metabolic panel
    - Participants were also assessed for HCC and liver-related events, including variceal bleeding, ascites, and spontaneous bacterial peritonitis related to cirrhosis

RESULTS

Participants

- 2,435 participants were enrolled from 25 different clinical studies (**Table 1**)
  - Participants were followed for a mean of 545 days (range, 1–1,334 days)
- HCC developed in 15 participants

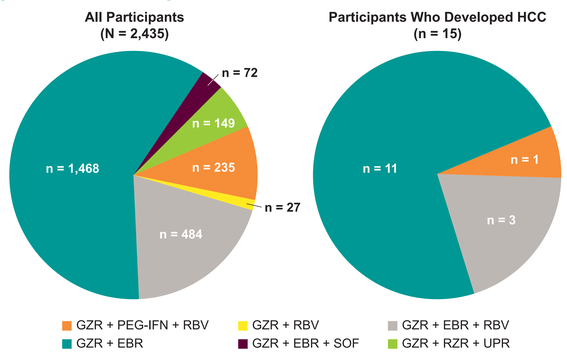
Table 1. Participant Demographics

Characteristic	All Participants N = 2,435	Participants With HCC n = 15
Achieved SVR12, n (%)	2,330 (95.7)	13 (86.7)
Male, n (%)	1,412 (58)	11 (73.3)
Race, n (%)		
White	1,815 (74.5)	8 (53.3)
Black	288 (11.8)	1 (6.7)
Asian	295 (12.1)	5 (33.3)
Hispanic/Latino, n (%)	203 (8.3)	0 (0)
Region of enrollment, n (%)		
North and South America	989 (40.6)	7 (46.7)
Europe	927 (38.1)	3 (20.0)
Asia-Pacific	519 (21.3)	5 (33.3)
BMI, mean (SD), kg/m^2	26.3 (4.8)	25.8 (5.3)
HCV genotype, n (%)		
GT1a	1,045 (42.9)	7 (46.7)
GT1b	1,073 (44.1)	8 (53.3)
GT2	59 (2.4)	0 (0)
GT3	92 (3.8)	0 (0)
GT1-other, 4, 5, or 6	166 (6.8)	0 (0)
Treatment history, n (%)		
Treatment-naive	1,811 (74.8)	9 (60.0)
Treatment-experienced	546 (22.4)	6 (40.0)
Age at initiation of HCV therapy, mean (SD), years	51.4 (11.1)	59.4 (7.1)
Cirrhosis (F4), n (%)	677 (27.8)	11 (73.3)
Baseline[a] APRI, median (range)	0.60 (0.10 to 22.30) [n = 2,003]	1.40 (0.30 to 4.90) [n = 13]
Baseline[a] FibroScan®, median (range)	7.8 (0.1 to 73.5) [n = 1,059]	22.1 (6.8 to 48.8) [n = 6]
Baseline[a] platelet count, mean (SD), 10^3 cells/μL	199.3 (66.2) [n = 693]	150.8 (108.7) [n = 4]
Baseline[a] albumin, mean (SD), g/dL	4.364 (0.337) [n = 668]	3.767 (0.611) [n = 3]
HCV/HIV coinfection, n (%)	217 (8.9)	0 (0)
History of alcohol use, n (%)	2 (0.1)	0 (0)
History of diabetes, n (%)	21 (0.9)	0 (0)

BMI, body mass index; GT, genotype; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation; SVR12, sustained virologic response rate at 12 weeks after completion of therapy.
[a]Values measured prior to start of GZR-containing regimen.

- Most participants received an all-oral GZR-containing DAA regimen (**Figure 1**)

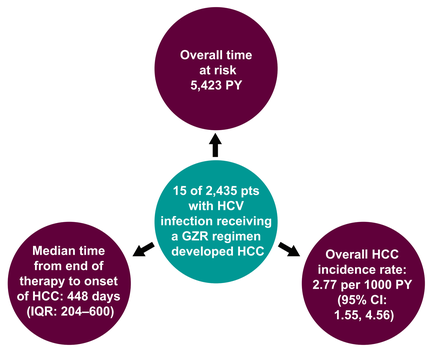
Figure 1. HCV Treatment Regimens



EBR, elbasvir; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; RZR, ruzasvir; SOF, sofosbuvir; UPR, uprifosbuvir.

- The overall HCC incidence rate was 2.77 per 1,000 person-years (**Figure 2**)

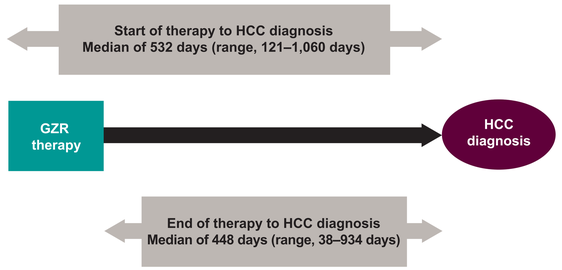
Figure 2. Incidence of HCC



CI, confidence interval; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; pts, participants; PY, person-years.

- Median time from start of DAA therapy to diagnosis of HCC was 532 days (range, 121–1,060 days) (**Figure 3**)

Figure 3. Time From DAA Therapy to Diagnosis of HCC[a]



DAA, direct-acting antiviral; GZR, grazoprevir; HCC, hepatocellular carcinoma.
[a]One participant who withdrew from treatment after 27 days had insufficient long-term follow-up data and was excluded from all analyses.

- Mean time from start of DAA therapy to diagnosis of HCC was 521.8 days (n = 13) and 670.0 days (n = 2) in participants who achieved sustained virologic response at 12 weeks after completion of therapy and those with virologic failure, respectively (**Table 2**)

Table 2. Time From DAA Therapy to Diagnosis of HCC According to Treatment Outcome

	Achieved SVR12 (n = 13)	Virologic Failure (n = 2)
Time from start of DAA therapy to HCC diagnosis, days		
Mean (SD)	521.8 (298.9)	670.0 (19.8)
Median (range)	447 (121–1,060)	670 (656–684)
Time from end of DAA therapy to HCC diagnosis, days		
Mean (SD)	429.4 (291.3)	586.0 (19.8)
Median (range)	363 (38–934)	586 (572–600)

DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; SD, standard deviation; SVR12, sustained virologic response at 12 weeks after completion of therapy.

- Development of HCC was significantly associated with the presence of cirrhosis (**Table 3**)
  - P = 0.0003 for the association between cirrhotic status and HCC (Fisher's Exact Test)

Table 3. Association Between Development of HCC and Cirrhosis Status

	HCC	No HCC
Cirrhosis, n	11	666
No cirrhosis, n	4	1,752

HCC, hepatocellular carcinoma.

- The characteristics of participants who developed HCC are shown in **Table 4**

Table 4. Characteristics of Participants Who Developed HCC

Participant	HCV Genotype	Baseline HCV RNA (×10^6 IU/mL)	Treatment and Medical History	Cirrhosis	Baseline Platelet Count (× 10^9/L)	*IL28B* Genotype	Treatment	Achieved SVR12	HCC Diagnosis	
									Time From Day 1 Therapy (months)	Time From End of Therapy (months)
71-year-old white male	GT1a	8.7	TN	Yes	172	CT	EBR/GZR × 18 weeks	Yes	35	31
55-year-old white male	GT1a	1.8	TE (PEG-IFN + RBV), DM	Yes (FS, 48.8 kPa)	63	CC	EBR/GZR × 12 weeks	Yes	15	12
55-year-old Asian male	GT1b	1.5	TN, DM	Yes (FS, 17.8 kPa)	116	CT	EBR/GZR × 12 weeks	Yes	21	18
54-year-old white female	GT1a	3.6	TN	No (cirrhosis detected at HCC Dx)	296	CT	EBR/GZR + RBV × 12 weeks	Yes	33	30
67-year-old white male	GT1a	0.3	TE (PEG-IFN + RBV)	Yes	65	CT	EBR/GZR + RBV × 18 weeks	Yes	12	8
56-year-old black male	GT1a	3.9	TN, past IV drug use, DM, hyperlipidemia	No	194	CT	GZR + PEG-IFN + RBV × 12 weeks	No	21	18
65-year-old white male	GT1b	0.6	TE (PEG-IFN + RBV), arterial sclerosis	Yes (FT, 0.88; plt 101,000 cells/ /μL)	101	CT	EBR/GZR × 12 weeks	Yes	24	21
59-year-old white male	GT1a	0.5	TN, hyperlipidemia, hypertension	Yes	162	CC	EBR/GZR × 12 weeks	No	22	19
55-year-old Asian female	GT1b	1.2	TN, DM, hyperlipidemia	Yes	63	CC	EBR/GZR × 12 weeks	Yes	27	23
68-year-old multiracial male	GT1a	9.1	TE (PEG-IFN + RBV), HCC (6 years prior), DM	No (FS, 6.8 kPa)	196	CT	EBR/GZR × 12 weeks	Yes	17	14
68-year-old white female	GT1b	0.9	TE (PEG-IFN + RBV), lymphoma (10 years prior)	Yes	75	TT	EBR/GZR × 16 weeks	Yes	14	10
55-year-old Asian male	GT1b	2.4	TN	Yes	112	CC	EBR/GZR × 12 weeks	Yes	9	6
45-year-old Asian male	GT1b	2.2	TN	Yes	141	CC	EBR/GZR × 12 weeks	Yes	11	8
51-year-old Asian male	GT1b	1.1	TN, liver and kidney cysts	No (METAVIR F2 on biopsy)	167	CC	EBR/GZR × 12 weeks	Yes	10	7
59-year-old white female	GT1b	2.1	TN	Yes (Child-Pugh class B)	90	CT	EBR/GZR × 12 weeks	Yes	6	3

DM, diabetes mellitus; Dx, diagnosis; EBR, elbasvir; FS, FibroScan®; FT, FibroTest; GT, genotype; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenous; PEG-IFN, pegylated interferon; plt, platelets; RBV, ribavirin; SD, standard deviation; TE, treatment-experienced; TN, treatment-naive.

CONCLUSIONS

- HCC is uncommon among participants who received a GZR-containing regimen for HCV infection
  - No clear association was observed between GZR therapy and the incidence of HCC
  - Participants who developed HCC were predominantly male and cirrhotic
  - Rates of HCC in the present study are similar to or lower than in previous reports, suggesting no correlation between GZR-containing regimens and HCC incidence[7-12]
- Limitations:
  - This is a post hoc analysis of an observational extension study
  - The data are limited to those participants who consented to have additional follow-up
    - The incidence of HCC in participants who did not enroll in the observational extension study is not known

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