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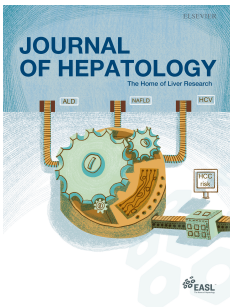

Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers high cure rate for hepatitis C virus retreatment in real-world settings

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Title: Glecaprevir/pibrentasvir + sofosbuvir + ribavirin offers high cure rate for hepatitis C virus retreatment in real-world settings

Short Title: G/P+SOF+RBV=High SVR in Real-World HCV Retreatment

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MM led and CC, LK and SP assisted with the study concept and design. MM and SP equally contributed to acquisition of data and analysis and interpretation of data. MM led initial drafting of the manuscript. All authors provided critical revision of the manuscript for important intellectual content, gave final approval of data, and are accountable for the work.

Abbreviations:

DAA = direct-acting antiviral

HCC = hepatocellular carcinoma

HCV = hepatitis C virus

SVR = sustained virologic response

Keywords: hepatitis C virus; direct-acting antivirals; retreatment; salvage therapy; glecaprevir/pibrentasvir, sofosbuvir, and ribavirin

To the Editor:

We read with interest the recent publication by Dietz et al: “Failure on voxilaprevir, velpatasvir, sofosbuvir and efficacy of rescue therapy” and would like to present additional data regarding salvage hepatitis C virus (HCV) treatment in this difficult-to-cure patient population.

Patients who fail to achieve sustained virologic response (SVR) with approved direct-acting antiviral (DAA) regimens have limited options for successful retreatment. Usage of a regimen containing an NS3/4A protease inhibitor, NS5A replication complex inhibitor, and NS5B polymerase inhibitor with weight-based ribavirin is appropriate for patients for whom even triple-DAA rescue therapy with sofosbuvir/velpatasvir/voxilaprevir did not achieve cure.

In 2018, the European Association for the Study of the Liver (EASL) guidelines first included a recommendation for the use of glecaprevir/pibrentasvir with sofosbuvir and ribavirin for up to 16 to 24 weeks in patients who had twice failed other DAA regimens.[1] Updated EASL guidelines published in 2020 recommend its use for 12-24 weeks in twice-failures of DAA regimens, and for 24 weeks in sofosbuvir/velpatasvir/voxilaprevir failures.[2] The joint American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) guidance first included this combination as a recommended retreatment option in November 2019. Since January 2021, American guidance recommends use of this regimen for 16 weeks in glecaprevir/pibrentasvir

failures and for 16-24 weeks in sofosbuvir/velpatasvir/voxilaprevir or glecaprevir/pibrentasvir plus sofosbuvir failures.[3]

Dietz, et al with the European Study Resistance Group, recently reported a 77% SVR rate in 13 sofosbuvir/velpatasvir/voxilaprevir failures who were retreated with glecaprevir/pibrentasvir, sofosbuvir, and ribavirin for 12–24 weeks.[4] Two case studies report SVR after 24 weeks of this regimen in two patients (HIV-coinfected genotype 1b, and genotype 3a), who had thrice-failed other DAA courses (the 3a patient had most recently failed sofosbuvir/velpatasvir/voxilaprevir).[5,6] One case report describes SVR after the on-treatment addition of sofosbuvir and ribavirin to glecaprevir/pibrentasvir in a treatment-naïve genotype 3a patient.[8] Treatment of 23 glecaprevir/pibrentasvir failures resulted in a 96% SVR rate after use of 12–16 weeks of this regimen as part of the MAGELLAN-3 phase IIIb clinical trial.[7] An HCV retreatment review article briefly references this trial and refers to this regimen as useful in some populations.[9] Authors are unaware of published reports of use of this regimen beyond these 39 patients; only 14 of whom had failed sofosbuvir/velpatasvir/voxilaprevir treatment.

This dual-center case series describes the use of glecaprevir/pibrentasvir with sofosbuvir and ribavirin as a salvage regimen in real-world settings in patients who previously failed multiple DAA regimens including sofosbuvir/velpatasvir/voxilaprevir.

Patients and Methods

Authors at two urban academic medical centers performed a retrospective review of the electronic medical records of DAA-experienced patients who initiated HCV treatment with glecaprevir/pibrentasvir plus sofosbuvir and ribavirin through April 10, 2020. The data collected included baseline demographics, medical history, HCV treatment-related details, and laboratory values throughout treatment and until SVR was achieved. This study was approved by both sites' institutional review boards. The primary outcome was SVR following treatment with glecaprevir/pibrentasvir, sofosbuvir, and ribavirin.

Results

Six patients began 16-24 weeks of HCV retreatment with glecaprevir/pibrentasvir, sofosbuvir, and ribavirin between July 2018 and March 2020. All patients achieved SVR. Baseline resistance was present in most patients (5/5 assessed for NS5A and 3/4 for NS3), and all had cirrhosis. No patients were on dialysis or had HIV or hepatitis B virus. No patients experienced serious adverse events or died during treatment. See Table 1 for additional patient details.

Weight-based ribavirin (1200mg/day; all patients weighed > 75 kg) was used for all patients based on authors' previous experience with the inclusion of ribavirin and extension of treatment length as methods for successful retreatment in DAA failures. Providers ordered complete blood counts and comprehensive metabolic panels every 2-4 weeks during HCV treatment. No patients had hemoglobin levels under 10 g/dL or required ribavirin dose adjustments during treatment.

Discussion

All patients treated with glecaprevir/pibrentasvir, sofosbuvir, and ribavirin achieved a cure. No patients died or had serious adverse events, implicating the safety of this regimen in our small cohort of patients. Providers are advised to monitor hemoglobin/hematocrit levels and renal function during the course of treatment that includes ribavirin and to counsel patients of childbearing potential on the importance of the use of two forms of contraception during therapy and for 6 months afterward due to the teratogenicity of ribavirin. Decompensated patients must be managed by a transplant center and closely monitored for elevated liver enzymes and further decompensation with off-label use of a protease inhibitor.

This salvage regimen lacks robust published clinical data. Patients were treated prior to the publication of the latest EASL and AASLD-IDSA guidelines, and treatment for 16 weeks was effective in 4 patients. This real-world case series adds to the available literature and demonstrates that salvage therapy with glecaprevir/pibrentasvir, sofosbuvir, and ribavirin is an effective and safe treatment for compensated cirrhotic patients who previously failed sofosbuvir/velpatasvir/voxilaprevir treatment .

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Table 1. Patient Characteristics

Patient	1	2	3	4	5	6
Age	67	60	61	68	68	58
Gender	Male	Male	Female	Male	Male	Male
Genotype	1b	3a	3	1a	1b	1a
Stage	Cirrhosis (CTP A)	Cirrhosis (CTP A)	Cirrhosis (CTP A)	Cirrhosis (CTP A)	Cirrhosis (CTP A)	Cirrhosis (CTP B)
Baseline History of HCC	No	Indeterminate liver lesions	No	Yes; received Y90 radioemboli zation	Yes; received Y90 radioemboli zation	No
Baseline NS5A resistance	T17S, T79A, Q288R, R311P, A347T, S396P, D403S	Y93H, S62T	no resistance panel available	K24K/E, M28T/M Q30R, Y93N	R30Q, L31V, Q54H, Y93H	L31V
Baseline NS3 resistance	Q80K	no resistance panel available	no resistance panel available	No mutations or resistance	Q80K/Q, D168V	V36M

				predicted		
Baseline HCV RNA (intl units/mL)	2,299,631	1,038,041	705,684	667,144	1,960,000	886,538
Regimen (length in weeks)[1]	G/P + SOF + RBV (16)	G/P + SOF + RBV (16)	G/P + SOF + RBV (16)	G/P + SOF + RBV; then G/P (24)[2]	G/P + SOF + RBV (24)	G/P + SOF + RBV (16)
Week 4 HCV RNA	-	**Detected, < 15** intl units/mL	-	**Not Detected**	**Not Detected**	**Not Detected**
End of Treatment HCV RNA	**Not Detected**	-	**Not Detected**	**Not Detected**	**Not Detected**	**Not Detected**
≥ 12 Weeks after Treatment HCV RNA	**Not Detected**	**Not Detected**	**Not Detected**	**Not Detected**	**Not Detected**	**Not Detected**
Failed Previous Regimens (length in weeks)						
Course 1:	LDV / SOF (12)	PegIFN + RBV (48)	SOF / VEL (12)	PegIFN + RBV + SOF (12)	PegIFN + RBV (48)	SOF / VEL (12)
Course 2:	SOF / VEL	SOF / VEL +	SOF /	LDV / SOF	SOF +	SOF / VEL /

	/ VOX (12)	RBV (12)	VEL / VOX + RBV (12)	(24)	SMV (12)	VOX (12)
Course 3:	-	SOF / VEL / VOX (12)	-	G/P (16)	LDV / SOF + RBV (24)	-
Course 4:	-	-	-	SOF / VEL / VOX + RBV (12)	SOF / VEL / VOX (12)	-

1. Ribavirin dose = 1200mg/day (dosed 600mg twice daily); all patients weighed > 75kg
2. Patient 4 received G/P + SOF + RBV for 13 weeks 4 days, then had a 14-day interruption due to orthotopic liver transplantation. SOF + RBV were discontinued after day 95 due to acute kidney injury post-transplant, but the patient received G/P through 24 weeks.

CTP = Child-Turcotte-Pugh; G/P = glecaprevir/pibrentasvir; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; LDV/SOF = ledipasvir / sofosbuvir; MELD-Na = Model for End-Stage Liver Disease - Sodium; PegIFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SMV = simeprevir; SOF = sofosbuvir; SOF/VEL = sofosbuvir / velpatasvir; SOF/VEL/VOX = sofosbuvir / velpatasvir / voxilaprevir