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Sofosbuvir, Glecaprevir, Pibrentasvir, and Ribavirin as a Rescue Therapy in Difficult-to-Treat HCV Patients

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Pangenotypic direct-acting antiviral (DAA) drugs have an HCV cure rate of >95% in almost all treated patients.[1,2] When DAA treatment fails, retreatment must be guided by virus resistance profiles, and phase 3 trials have reported sustained virological responses (SVR) of 96%-98% after a 12-week course of sofosbuvir (SOF), velpatasvir (VEL), and voxilaprevir (VOX).[3] However, the management is more uncertain after SOF/VEL/VOX failure, and there is still insufficient evidence to support a particular retreatment. For instance, Dietz et al.[4] reported 77% SVR at 12 weeks (SVR12) in patients with different HCV profiles retreated with glecaprevir (GLE)/pibrentasvir (PIB), SOF, and ribavirin (RBV) for 12-24 weeks after SOF/VEL/VOX failure.

Clinical Observation

The characteristics of 5 patients treated at three tertiary care hospitals who failed a 12-week course of SOF/VEL/VOX rescue therapy for chronic HCV are shown in Table 1. Four out of 5 (80%) patients were male and had Child-Turcotte-Pugh (CTP) compensated cirrhosis, 2 of 5 (40%) had clinically significant portal hypertension (CSPH) as defined by the presence of esophageal varices on gastroduodenal endoscopy, and 1 had hepatocellular carcinoma (HCC). Three out of 5 (60%) had HCV genotype 3, 1 (20%) had genotype 1b, and 1 (20%) had genotype 4d. Eighty percent of patients had previously been treated with DAAs: 2 had received SOF and daclatasvir for 24 weeks and 2 had received SOF and ledipasvir for 12 weeks prior to SOF/VEL/VOX treatment.

Baseline resistance-associated substitution (RAS) results prior to SOF/VEL/VOX retreatment were available in 4 patients and showed nonstructural protein 5A (NS5A) RAS at position Y93H in 2 (50%) patients with genotype 3 HCV and no RASs in 1 patient; NS3A or NS5B RASs were not detected. RAS testing was also conducted after SOF/VEL/VOX treatment, and there were no changes in RAS status in any patient. All 5 patients were retreated with combined SOF and GLE/PIB with RBV for 16 weeks, and all (100%) achieved an SVR. Tolerance and adherence were excellent.

The 2 patients with CSPH and the patient with HCC had compensated CTP A cirrhosis with a Model for End-Stage Liver Disease (MELD) score <10. They were monitored for adverse events monthly by clinical examination and standard blood test. The patient with HCC also underwent a CT scan

Abbreviations: ALT, alanine aminotransferase; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; DAA, direct-acting antiviral; GLE, glecaprevir; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; NS, nonstructural protein; PEG-IFN, pegylated interferon; PIB, pibrentasvir; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir.

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TABLE 1. Patient characteristics (n = 5)

Characteristic	Value
Age (years)	56.5 ± 4.9
Male, n (%)	4 (80)
HCV genotype, n (%)	
1b	1 (20)
3	3 (60)
4d	1 (20)
Treatment regimen prior to SOF/VEL/VOX, n (%)	
SOF/LDV	2 (40)
SOF/DCV/RBV	2 (40)
PEG-IFN	1
RAS testing prior to SOF/VEL/VOX, n (%)	
NS5A RAS at position Y93H	2 (40)
No RAS	2 (40)
Not tested	1 (20)
RASs after SOF/VEL/VOX failure, n (%)	
NS5A RAS at position Y93H	2 (40)
No RAS	2 (40)
Not tested	1 (20)
Cirrhosis Child-Pugh score A, n (%)	4 (80)
Fibrosis F2, n (%)	1 (20)
Clinical portal hypertension, n (%)	2 (40)
HCC, n (%)	1 (16.6)
SVR after SOF+GLE/PIB+RBV treatment	5 (100)

Abbreviations: DCV, daclatasvir; HCC, hepatocellular carcinoma; LDV, ledipasvir; NS, nonstructural protein; PEG-IFN, pegylated interferon; RASs, resistance-associated substitutions.

3 months after retreatment. CTP and MELD scores did not worsen during treatment. Two patients died after achieving SVR, 1 from metastasis from the HCC diagnosed prior to salvage treatment and 1 from an extrahepatic cause.

Discussion

There are currently no clinical guidelines to support decision-making when retreating patients failing SOF/VEL/VOX rescue therapy. Genotype 3 HCV, consistent with 3/5 of our patients, is more likely to be difficult to treat. While Bourlière et al.[3] reported that 95% of genotype 3 patients treated with SOF/VEL/VOX achieved an SVR, the study only included a few genotype 3 infections in patients with cirrhosis, making it difficult to generalize results in this subgroup.

Interestingly, although treatment-emergent RASs can occur, we did not detect any RAS changes after SOF/VEL/VOX therapy. The only detected RAS was a substitution at NS5A amino acid position 93, which is known to confer a high level of resistance to NS5A inhibitors like velpatasvir. However, this substitution is still susceptible to PIB,[5] motivating our choice of retreatment. In contrast to Dietz et al.,[4] our patients received 16 weeks of treatment as standard (versus 12-24 weeks), resulting in an SVR12 of 100%. Furthermore, we only included patients with compensated liver disease as protease inhibitors are contraindicated in decompensated cirrhosis.

Our observations confirm that SOF/GLE/PIB/RBV represents a promising alternative rescue treatment when SOF/VEL/VOX fails, and further studies are necessary to validate this therapeutic option.

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