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Epclusa® (SOF/VEL) Use in Hepatocellular Carcinoma

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) in patients with hepatocellular carcinoma (HCC).

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Clinical Data on the Use of SOF/VEL in HCC

Randomized Controlled Trial of SOF/VEL in HCC[1]

Study design and demographics

A prospective, randomized controlled trial compared the 1-year RFS of participants with HCV-related HCC who received a 12-week regimen of SOF/VEL after successful radiographic ablation with that of participants whose DAA therapy was postponed for ≥12 months after tumor ablation (postponed DAA group). All participants (N=84) had 1 to 3 HCC lesions that measured ≤5 cm with no extra-hepatic or vascular involvement and were not candidates for liver resection or transplant. Participants with CP Class B also received RBV or, if they could not tolerate RBV, extended SOF/VEL treatment to 24 weeks. Prior DAA exposure or locoregional treatment for HCC, presence of hepatitis B surface antigen, CP Class C, and INR >1.5 were among the exclusion criteria.

Table 1. Baseline Demographics and Disease Characteristics (Kamal et al)[1]

Key Demographics and Characteristics		SOF/VEL (n=43)	Postponed DAA (n=41)
Age, mean ± SD, years		54.98±8.39	57.78±7.77
Male, n (%)		34 (79.1)	32 (78)
Number of HCC lesions, n (%)	1	34 (79.1)	28 (68.3)
	2	7 (16.3)	13 (31.7)
	3	2 (4.7)	0
CP class, n (%)	A	31 (72.1)	30 (73.2)
	B	12 (27.9)	11 (26.8)
Serum albumin, median (IQR), g/dL		3.4 (3.1–3.6)	3.2 (3–3.6)
TB, median (IQR), mg/dL		1.1 (0.92–1.4)	1.14 (0.88–1.87)
ALT, median (IQR), U/L		49 (34–87)	61.3 (48–93.5)
AST, median (IQR), U/L		65 (46–98)	54 (35–85)

Results

In the SOF/VEL group, the SVR12 rate was 86.1% (37/43). There were no HCV relapses. At 1 year of follow-up, the overall RFS rate was significantly greater in the SOF/VEL group than in the postponed DAA group (*P*<0.001; Table 2).

Table 2. Tumor Recurrence and Liver Health at 1-Year Follow-Up (Kamal et al)[1]

Parameter		SOF/VEL (n=43)	Postponed DAA (n=41)
Overall tumor recurrence at 1 year, n		11	25
<3 cm		5	8
3–4 cm		3	12
>4 cm		3	5
Local tumor recurrence at 1 year, n		2	6
<3 cm		0	0
3–4 cm		0	4
>4 cm		2	2
Overall RFS at 1 year,[a] %		72.2	38
Estimated recurrence-free time, mean, months		10.6	8.18
Local RFS, %		95.3	84.8
Estimated recurrence-free time, mean, months		11.6	11.2
CP class change,[b] n	A to B	6	6
	B to C	0	6
	B to A	6	0

[a]*P*=0.001. [b]*P*=0.01.

There were 6 deaths in the SOF/VEL group (HCC, n=4; liver failure, n=2) and 5 in the postponed DAA group (HCC, n=4; liver failure, n=1). Kaplan-Meier estimates of 1-year overall survival rates in the SOF/VEL and postponed DAA groups were similar: 85.8% and 87.6%, respectively (*P*=0.752). Vascular invasions developed in 3 participants in the SOF/VEL group and in 1 participant in the postponed DAA group. There were no lymphatic or distant metastases.

Multivariate analysis showed that lower HCC recurrence 1 year after ablation was significantly associated with receipt of SOF/VEL (HR, 0.4; 95% CI: 0.189–0.846; *P*=0.016) and higher albumin levels at baseline (HR, 0.161; 95% CI: 0.058–0.453; *P*=0.001).

Real-World Data on the Use of SOF/VEL in HCC

Taiwanese Registry Analysis[2]

Study design and demographics

Real-world safety data from 7677 patients who registered in a Taiwanese HCV registry (August 2019–August 2021) and who received ≥1 dose of a 12-week regimen of SOF/VEL (68.1%) or an 8- to 12-week regimen of GLE/PIB (31.9%) were evaluated. Patients were followed for ≥3 months after the end of treatment.

Overall, patients were a mean of 59.6 years old, and 53% were male. At baseline, 283 patients (3.7%) had HCC.

Results

The SVR12 rate was 92.8% (7128/7677) in the overall population (PP population, 99.1%; 7128/7188). Grade 2 to 4 laboratory abnormalities of elevations in levels of ALT, AST, or TB occurred in 146 patients (1.9%). The presence of HCC was a significant risk factor for developing laboratory abnormalities in the overall population (*P*<0.01; Table 3), in SOF/VEL-treated patients (multivariate OR, 2.76; 95% CI: 1.3–5.84; *P*<0.01), and in GLE/PIB-treated patients (multivariate OR, 2.38; 95% CI: 1.08–5.25; *P*=0.03). Presence of HCC was also reported as a significant risk factor for Grade 2 to 4 laboratory abnormalities of TB elevations in the overall population (*P*<0.01) and in the GLE/PIB-treated patients (multivariate OR, 2.51; 95% CI: 1.12–5.61; *P*=0.03), but not in the SOF/VEL-treated patients. No such relationship was identified for individual evaluations of ALT or AST abnormalities.

Table 3. Rates and Risk Factors for Grade 2 to 4 Laboratory Abnormalities (Yu et al)[2,3]

Laboratory Parameter		SOF/VEL (n=5228), n (%)	GLE/PIB (n=2449), n (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
ALT, AST, or TB	Overall	54 (1)	92 (3.8)	3.74 (2.66–5.25)[a]	4.76 (3.33–6.8)[a]
	HCC	11 (5.1)	9 (13.4)	4.39 (2.69–7.14)[b]	2.63 (1.54–4.5)[b]
		20 (7.1)			
	No HCC	43 (0.9)	83 (3.5)		
		126 (1.7)			
ALT	Overall	12 (0.2)	9 (0.4)	1.6 (0.67–3.81)[c]	–
	HCC	2 (0.7)		2.76 (0.64–11.91)[d]	–
	No HCC	19 (0.3)			–
AST	Overall	8 (0.2)	7 (0.3)	1.87 (0.68–5.16)[c]	–
	HCC	1 (0.4)		1.87 (0.24–14.26)[d]	–
	No HCC	14 (0.2)			–
TB	Overall	40 (0.8)	82 (3.4)	4.49 (3.07–6.58)[e]	6.02 (4.02–9.01)[e]
	HCC	18 (6.4)		4.76 (2.84–7.97)[b]	2.74 (1.55–4.85)[b]
	No HCC	104 (1.4)			

[a]*P*<0.01 for comparisons between GLE/PIB vs SOF/VEL, regardless of HCC.
[b]*P*<0.01 for comparisons between HCC vs no HCC in the overall population.
[c]Nonsignificant for comparisons between GLE/PIB vs SOF/VEL, regardless of HCC.
[d]Nonsignificant for comparisons between HCC vs no HCC in overall population.
[e]*P*<0.01 for comparisons between GLE/PIB vs SOF/VEL.

A separate analysis was done in participants who developed Grade 3 or 4 laboratory abnormalities. Of the patients who developed Grade 3 to 4 laboratory abnormalities of elevations in ALT, AST, or TB levels, all 7 patients in the SOF/VEL cohort and 10 of the 11 patients in the GLE/PIB cohort had HCC. Although the presence of HCC was not a significant risk factor, treatment with GLE/PIB vs SOF/VEL was associated with the development of Grade 3 or 4 laboratory abnormalities in ALT, AST, or TB levels (multivariate OR, 3.77; 95% CI: 1.45–9.78; *P*=0.01).

South Korean Study[4]

Study design and demographics

A real-world study was conducted to evaluate the effectiveness and safety of SOF/VEL in 37 patients with HCV who were considered difficult to treat due to prior DAA failure, decompensated cirrhosis, or presence of HCC.

Table 4. Baseline Demographics and Disease Characteristics (Woo et al)[4]

Key Demographics and Characteristics		SOF/VEL (N=37)
Age, median (range), years		65 (45–83)
Male, %		59.5
HCV RNA, median (range), IU/mL		852,500 (11,100–10,800,000)
HCV genotype, 1/2/1b or 2b, %		67.6/29.7/2.7
HCC, %		37.8
Barcelona Clinic Liver Cancer Stage, A/B/C, %		4/8/2
Cirrhosis, %		56.8
Decompensated cirrhosis, %		7.5
Previous DAA treatment, n (%)	DCV + ASV	16 (43)
	SOF + RBV	11 (29.7)
	GLE/PIB	3 (8)
	LDV/SOF	1 (2.7)
	BOC	1 (2)

Abbreviations: ASV=asunaprevir; BOC=boceprevir; DCV=daclatasvir; LDV=ledipasvir.

Results

The SVR12 rate was 97.2% (36/37) in the ITT population and 100% (36/36) in the PP population. One patient died during treatment due to HCC progression. Most patients tolerated treatment with SOF/VEL well and did not experience adverse events.

Abbreviations

CP=Child-Pugh
DAA=direct-acting antiviral
GLE=glecaprevir
HCC=hepatocellular carcinoma
HR=hazard ratio
OR=odds ratio
PIB=pibrentasvir
PP=per protocol
RBV=ribavirin
RFS=recurrence-free survival
SOF=sofosbuvir
SVR12=sustained virologic response 12 weeks after end of treatment
TB=total bilirubin
VEL=velpatasvir

References

1. Kamal A, Metawea M, Omar H, Ghallab M, Kassem A, Naguib H. Hepatitis C Virus-Related One-Year Hepatocellular Carcinoma Recurrence After Directly Acting Antivirals: A Randomized Controlled Trial. *J Gastrointest Cancer.* 2024;55(2):913-923.
2. Yu ML, Tai CM, Mo LR, et al. An algorithm for simplified hepatitis C virus treatment with non-specialist care based on nation-wide data from Taiwan. *Hepatol Int.* 2024;18(2):461-475.
3. Yu ML, Tai CM, Mo LR, et al. An algorithm for simplified hepatitis C virus treatment with non-specialist care based on nation-wide data from Taiwan [Supplementary Materials]. *Hepatol Int.* 2024;18(2):461-475.
4. Woo HY, Heo J, Park YJ. Real-life effectiveness and safety of sofosbuvir/velpatasvir in difficult to treat hepatitis C patients [Abstract FRI392]. *Journal of Hepatology.* 2022;77(S1):S586.

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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