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Sofosbuvir/velpatasvir for patients with chronic genotype 3 HCV infection with compensated cirrhosis: Response to EASL Recommendations on Treatment of Hepatitis C 2018

To the Editor:

The recently published "EASL Recommendations on Treatment of Hepatitis C 2018" are described as "primarily based on evidence from existing publications and presentations at international meetings." We agree with this approach that prioritizes publically available clinical data from randomized clinical trials over personal experience or preclinical information; however, the current guidelines have overlooked relevant phase III results that have been published in peer-reviewed journals and/or presented at internationally recognized meetings regarding the use of sofosbuvir/velpatasvir for patients with chronic genotype 3 HCV infection with compensated cirrhosis. These results have been subsequently confirmed by data from real-world cohorts which provide additional support for the use of this ribavirin-free, single-tablet regimen in this important difficult-to-cure patient population.

Sofosbuvir/velpatasvir for 12 weeks has been evaluated in 236 genotype 3 HCV-infected patients with compensated cirrhosis enrolled in 5 phase III clinical trials (Table 1). The phase III trials include dedicated studies of patients with genotype 3 HCV infection, namely GS-US-342–1140 and GS-US-367–1173, as well as other studies which enrolled patients of all genotypes based on the pangenotypic activity of sofosbuvir/velpatasvir, GS-US-342–1202 which enrolled patients with HCV/HIV coinfection and GS-US-342–1521 and GS-US-342–1522 which are regional registrational studies conducted in India and Russia and Sweden, respectively.[1–5] Across these phase III studies, 95% (224/236, 95% CI 91–97%) of genotype 3 HCV-infected patients with cirrhosis achieved sustained virologic response 12 weeks post-treatment (SVR12). Importantly, of the 12 patients who did not achieve SVR12, 8 patients relapsed, 2 others had drug levels consistent with nonadherence, 1 was lost to follow-up and 1 discontinued treatment after 6 doses due to an adverse event. Therefore, the overall relapse rate was 3% from these phase III trials.

Coincident with the publication of the EASL recommendations, a large phase II study enrolling only patients with HCV genotype 3 and cirrhosis was presented at the International Liver Conference and subsequently published.[6] In this trial, patients were randomized to receive sofosbuvir/velpatasvir with or without ribavirin for 12 weeks. Among the patients treated with sofosbuvir/velpatasvir, 91% (92/101) achieved SVR12 with 5 patients experiencing virologic relapse (relapse rate 5%), 2 lost to follow-up, 1 non-response and 1 discontinuation due to an adverse event. In the treatment group receiving sofosbuvir/velpatasvir with ribavirin, 96% (99/103) patients achieved SVR12 with 2 patients experiencing virologic relapse (relapse rate 2%) and 2 lost to follow-up. The benefit of the addition of ribavirin to the regimen was largely attributable to the difference in relapse rates among patients with baseline NS5A resistance-associated substitutions. The trial was not powered to assess non-inferiority of the two treatment arms, and the numeric difference in relapse rate between the two treatment arms does not suggest a clinically meaningful difference in outcome, particularly when interpreted in the context of the phase III data described above.

The high SVR12 rate observed in clinical trials assessing sofosbuvir/velpatasvir for 12 weeks in genotype 3 HCV-infected patients with cirrhosis has now also been confirmed in real-world settings. The largest of the studies to date have come from an Italian regional registry and the German Hepatitis C Cohort[7–9] (Table 1). Overall, sofosbuvir/velpatasvir for 12 weeks in patients with genotype 3 and cirrhosis resulted in a SVR12 rate of 95% (91/96, 95% CI 88–98%), 95% in Italy (71/75, personal communication) and 95% in Germany (20/21).

One of the EASL-recommended regimens for patients with genotype 3 HCV infection and compensated cirrhosis is glecaprevir/pibrentasvir for 12 or 16 weeks based on prior treatment experience. The referenced presentation reported SVR12 rates of 99% (64/65, 95% CI 92–100%) in treatment-naive patients with cirrhosis treated for 12 weeks, and 94% (48/51, 95% CI 84–99%) in treatment-experienced patients with cirrhosis treated for 16 weeks.[10] The combined point estimate and confidence intervals of SVR12 results for these two durations (97% (112/116), 95% CI 91%–99%) overlap with those from the larger phase II and phase III datasets with sofosbuvir/velpatasvir for 12 weeks (94% (316/337), 95% CI 91%–96%). Real-world data in genotype 3 HCV-infected patients with cirrhosis are not yet available for glecaprevir/pibrentasvir.

Given the considerable clinical data from HCV trials published over the last several years, the challenges, when formulating clinical guidelines, of accounting for all relevant studies for the many regimens now available are acknowledged. However, the clinical and real-world data clearly support the use of sofosbuvir/velpatasvir for 12 weeks in patients with HCV genotype 3 and compensated cirrhosis, and this regimen should be recommended in this population. Although the addition of ribavirin to sofosbuvir/velpatasvir may increase SVR rates among patients with certain baseline NS5A resistance-associated substitutions, the efficacy data of sofosbuvir/velpatasvir

Table 1. SVR12 rate for patients with genotype 3 and compensated cirrhosis treated with sofosbuvir/velpatasvir for 12 weeks.

	SVR12, % (n/N)
Phase III trial data	
GS-US-342–1140 (ASTRAL-3; Foster GR *et al.*[1])	91 (73/80)
GS-US-367–1173 (POLARIS-3; Jacobson IM *et al.*[2])	96 (105/109)
GS-US-342–1202 (ASTRAL-5; Wyles D *et al.*[3])	100 (3/3)
GS-US-342–1521 (India Regional; Sood A *et al.*[4])	97 (32/33)
GS-US-342–1522 (Russia and Sweden Regional; Weiland O *et al.*[5])	100 (11/11)
Total	95 (224/236)
Real-world data	
Italian Regional Registry (Mangia A, *et al.*[7,8])	95 (71/75)
GECCO (von Felden J *et al.*[9])	95 (20/21)
Total	95 (91/96)

SVR12, sustained virologic response 12 weeks post-treatment.

without ribavirin across heterogeneous populations with diverse geographic and baseline characteristics indicate that ribavirin is not needed to achieve high SVR rates among genotype 3 HCV-infected patients with compensated cirrhosis. Furthermore, the 12-week, single-tablet regimen of sofosbuvir/velpatasvir currently approved in 54 countries is a highly effective treatment for all patients with compensated liver disease, irrespective of genotype, extent of liver fibrosis or prior interferon treatment history, and is an important tool in achieving the goal of HCV elimination as set forth by the World Health Organization and wholly embraced by EASL. As such, clinical practice guidelines should reflect the data in its totality.

Conflict of interest

All authors are employees of and hold stock interest in Gilead Sciences, Inc.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.08.029.

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Reply to: "Sofosbuvir/velpatasvir for patients with chronic genotype 3 HCV infection with compensated cirrhosis: Response to EASL recommendations on treatment of Hepatitis C 2018"

EASL Recommendations on Treatment of Hepatitis C 2018: Precision on the treatment of patients with genotype 3a infection and compensated cirrhosis

To the Editor:

The European Association for the Study of the Liver (EASL) read with interest the letter to the Editor by Stamm *et al.* The authors of the letter conclude that "the 12-week, single-tablet regimen of sofosbuvir/velpatasvir [...] is a highly effective treatment for all patients with compensated liver disease, irrespective of genotype, extent of liver fibrosis or prior interferon treatment history". This statement is too simplistic as the combination of sofosbuvir and velpatasvir without ribavirin is suboptimal in patients with cirrhosis infected with HCV genotype 3 carrying the Y93H resistance-associated substitution (RAS) in the NS5A region of the viral genome at treatment baseline.

A recent study of *in vitro* resistance of recombinant genotype 3a infectious viruses in cell culture showed intermediate-level resistance to velpatasvir (80–999-fold increase in the efficacious concentration 50% [EC50]) to be conferred by the Y93H RAS alone, whereas high-level resistance (≥1,000-fold increase in EC50) was conferred when the Y93H RAS occurred in combination with other NS5A RASs, in particular at position L31.[1] These *in vitro* data have been substantiated by reports of a lower