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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Luisa M. Stamm*
Diana M. Brainard
John G. McHutchison
Gilead Sciences, Inc., Foster City, CA, United States
*Corresponding author. Address: Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404, United States. Tel.: +1 650 574 3000.
E-mail address: Luisa.stamm@gilead.com

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

responsiveness to sofosbuvir/velpatasvir in patients infected with genotype 3 viruses carrying the Y93H RAS than in those infected with wild-type HCV. In the ASTRAL-3 phase III trial, the sustained virological response (SVR) rates after 12 weeks of sofosbuvir/velpatasvir were 97% (225/231) in patients without NS5A RASs at baseline *vs.* 88% (38/43) in those with detectable NS5A RASs at baseline. Treatment failures associated with NS5A RASs were observed in both treatment-experienced patients without cirrhosis and treatment-naïve and treatment-experienced patients with compensated cirrhosis.[2]

These data were the basis for the 2016 EASL Recommendations on Treatment of Hepatitis C for genotype 3a-infected patients with compensated cirrhosis:[3] "If no NS5A resistance testing is performed, [...] treatment-naïve and treatment-experienced patients with compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively).".[3] This recommendation allowed for the fact that the vast majority of prescribers do not have access to HCV resistance testing. However, EASL also recommended that "if reliable NS5A resistance testing is performed, [...] treatment-naïve and treatment-experienced patients with compensated cirrhosis with the NS5A RAS Y93H detectable at baseline should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RAS Y93H at baseline should receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin".[3]

These recommendations have subsequently been supported by a randomized controlled trial of sofosbuvir and velpatasvir with or without ribavirin in genotype 3-infected patients with compensated cirrhosis.[4] In this study, patients with genotype 3 infection and compensated cirrhosis were assigned to receive sofosbuvir and velpatasvir for 12 weeks or sofosbuvir and velpatasvir plus ribavirin for 12 weeks. Although the study was not powered to show a significant difference, there were 6/101 (5.9%) virological failures in the no ribavirin arm *vs.* 2/103 (1.9%) in the ribavirin-containing arm. In the sofosbuvir and velpatasvir without ribavirin arm, the proportion of patients with baseline NS5A RASs who achieved an SVR was numerically smaller than that of patients without NS5A RASs (84% *vs.* 96%, respectively). In the sofosbuvir and velpatasvir plus ribavirin arm, baseline NS5A RASs had less effect on the proportion of patients with an SVR (96% *vs.* 99%, respectively).[4]

In the POLARIS-3 trial, the SVR rate was 96% (105/109) after 12 weeks of sofosbuvir/velpatasvir in the control arm. However, there were only 4 patients with the Y93H RAS (who all achieved SVR) in this arm.[5] When pooling the results of ASTRAL-3, POLARIS-3 and the randomized controlled trial in patients with cirrhosis, the SVR rates after sofosbuvir/velpatasvir without ribavirin were 73/81 (90%) in patients with any NS5A RAS, and only 27/33 (82%) in patients with the Y93H RAS.[2,4,5]

With the objective of achieving the elimination of hepatitis C as a public health threat by 2030, the EASL Recommendations on Treatment of Hepatitis C aim at guaranteeing the broadest possible access to the best possible HCV care. For this, simplification of the care cascade, limited monitoring and minimization of side effects are essential. Thus, treatment regimens requiring ribavirin were excluded from the 2018 version of the EASL Recommendations on Treatment of Hepatitis C (with the exception of patients with decompensated cirrhosis for whom protease inhibitors are contraindicated). In addition, HCV resistance testing prior to first-line direct-acting antiviral (DAA)-based therapy was not recommended because the technology is not available to the vast majority of treating physicians worldwide.[6] As a result, the triple combination of sofosbuvir, velpatasvir and voxilaprevir was recommended instead of sofosbuvir/velpatasvir plus ribavirin in patients infected with genotype 3 with compensated cirrhosis.[6] This recommendation was based on the results of the POLARIS-2 and POLARIS-3 Phase III trials showing 99% (91/92) and 96% (106/110) SVR rates after only 8 weeks of treatment with this regimen, respectively.[5] Because genotype 3 is more difficult-to-cure than other genotypes, and in the absence of data with 12 weeks of therapy, it appeared to be safer to recommend treating patients with genotype 3 infection who have cirrhosis for 12 weeks with this combination. The recommendation is supported by a recent editorial suggesting that sofosbuvir/velpatasvir/voxilaprevir is preferable to sofosbuvir/velpatasvir in any situation in which ribavirin might be under consideration (except for patients with decompensated cirrhosis for which voxilaprevir is contraindicated).[7]

The 2018 EASL recommendations indicate that, in settings where sofosbuvir/velpatasvir/voxilaprevir is not available or not affordable, "options proposed in previous versions of [the] recommendations remain acceptable for patients likely to respond to these regimens until new DAAs become available and affordable". The 2018 recommendations also indicate that, although they "suggest treatment regimens that do not necessitate any resistance testing prior to first-line therapy [...], physicians who have easy access to reliable resistance tests can use these results to guide their decisions [...].".[6] Therefore, in areas where sofosbuvir/velpatasvir/voxilaprevir is not available or not affordable, patients with genotype 3 infection and compensated cirrhosis should be treated with sofosbuvir/velpatasvir plus weight-based ribavirin for 12 weeks if no NS5A resistance testing is performed; however, if reliable NS5A resistance testing is available and performed, only patients with the Y93H RAS should receive ribavirin, whereas the remaining patients can be treated with sofosbuvir/velpatasvir alone for 12 weeks. In areas where sofosbuvir/velpatasvir/voxilaprevir is available, if reliable NS5A resistance testing is performed prior to therapy, only patients with the Y93H RAS should be treated with sofosbuvir/velpatasvir/voxilaprevir, whereas patients without NS5A RASs can be treated with sofosbuvir/velpatasvir alone for 12 weeks.

In the absence of head-to-head comparisons, careful interpretation of future clinical trials and somewhat heterogeneous real-world studies will be required in patients infected with genotype 3, especially those with cirrhosis. In particular, the exact prevalence of baseline NS5A RASs (including the Y93H RAS) and their influence on the SVR will need to be provided in areas of low and high Y93H prevalence. Indeed, studies performed in areas of low prevalence of the Y93H RAS may bias the results in favor of the two-drug combination. For instance, in the German real-world study cited by Stamm *et al.*, there was only one patient with genotype 3 and cirrhosis with the Y93H RAS at baseline; this patient achieved SVR after a 12-weeks course of sofosbuvir/velpatasvir plus ribavirin.[8] In such regions, it may appear that first-line therapy with sofosbuvir/velpatasvir in GT3 infected patients is reasonable.

In order to ensure wide applicability of its HCV treatment recommendations, EASL opted for the safest, most efficacious

Table 1. Treatment indications in treatment-naïve and treatment-experienced patients (as defined in the recommendations) infected with HCV genotype 3 with compensated cirrhosis according to the availability of HCV resistance testing, as per the 2018 EASL Recommendations on Treatment of Hepatitis C [6].

Patients infected with HCV genotype 3 with compensated cirrhosis				
Availability/ performance of HCV NS5A resistance testing	**Results of HCV NS5A resistance testing***	**Sofosbuvir/velpatasvir-based regimen**		**Glecaprevir/pibrentasvir-based regimen**
		Sofosbuvir/velpatasvir/ voxilaprevir available: apply 2018 EASL recommendations	**Sofosbuvir/velpatasvir/ voxilaprevir not available: apply 2016 EASL recommendations**	**Glecaprevir/pibrentasvir available: apply 2018 EASL recommendations**
Not available/not performed	–	Sofosbuvir/velpatasvir/ voxilaprevir for 12 weeks	Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°
Available and performed	Presence of the Y93H RAS at baseline	Sofosbuvir/velpatasvir/ voxilaprevir for 12 weeks	Sofosbuvir/velpatasvir plus ribavirin for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°
	No Y93H RAS at baseline	Sofosbuvir/velpatasvir for 12 weeks	Sofosbuvir/velpatasvir for 12 weeks	Glecaprevir/pibrentasvir for 12 weeks in treatment-naïve or 16 weeks in treatment-experienced patients°

EASL, European Association for the Study of the Liver; RAS, resistance-associated substitution.
* The presence of the NS5A RAS Y93H at baseline is by population sequencing or >15% by deep sequencing.
° Data with 12 weeks of treatment with glecaprevir and pibrentasvir in treatment-experienced patients with cirrhosis are needed.

and most universal treatment indications. EASL acknowledges the depth of detail in the 2018 recommendations: numerous tables and layers of evidence were provided.[6] To clarify, 3 regimens are recommended in the guidelines for the treatment of patients infected with genotype 3: sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, or glecaprevir/pibrentasvir. The indications for genotype 3-infected patients with compensated cirrhosis are summarized in Table 1.

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European Association for the Study of the Liver *
*Corresponding author. Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 228070360; fax: +41 (0) 223280724.

Acute liver failure due to immune-mediated hepatitis successfully managed with plasma exchange: New settings call for new treatment strategies?

To the Editor:

We read with great interest the recent article by De Martin *et al.* characterizing the liver injury induced by cancer immunotherapy. Their experience in immune-mediated hepatitis related to checkpoint inhibitors included 16 histologically proven cases after anti-PD-1/PD-L1 or anti-CTLA-4 therapy; in 38%, hepatitis resolved without steroid therapy.[1] However, as illustrated by the case recently reported by Bhave *et al.*, immune-mediated hepatitis can be severe and lead to acute liver failure (ALF), with a poor prognosis despite treatment with high steroid doses plus mycophenolate mofetil (MMF).[2] The oncological context of

Keywords: Immune-mediated hepatitis; Acute liver failure; Plasma exchange; Immunotherapy.