velpatasvir with weight-based ribavirin for 12 weeks has less favorable efficacy in genotype 3b patients (reported previously2), as mentioned in the present EASL recommendations3 and the Taiwan consensus statement on the management of hepatitis C, 2020.3 As such, we believe that the recommendation for a S-Gf-P regimen of sofosbuvir/velpatasvir need to be limited to treatment-naïve GT-3 patients without cirrhosis. Sofosbuvir-containing regimens can be used in patients with renal diseases, including those with an eGFR ≤30 mL/min and those with end-stage renal disease on hemodialysis, based on previous guidance,4,5 with no need for dose adjustments of DAAs.6,7 Thus, these patients are considered eligible for S-Gf-P regimens. Under the circumstances, evaluation of renal function does not seem necessary if applying S-Gf-P anti-HCV treatments.

Lastly, we believe that it may be inadequate to omit the tests for sustained virologic response (SVR) even with the very high SVR12 rates expected with these regimens, as determining treatment response is crucial for the further management of patients, particularly for those with advance fibrosis or cirrhosis.1,2,3

Financial support
The authors received no financial support to produce this manuscript.

Conflict of interest
CY Dai: Consultant of Gilead, Abbvie; Speaker of Gilead, Abbvie and Merck. WL Chuang: Speaker of Gilead and Abbvie. ML Yu: Research support (grant) from Gilead and Abbott; Consultant of Gilead, Abbvie and Merck; Speaker of Gilead, Abbvie and Merck.

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

Authors’ contributions
Chia-Yen Dai and Ming-Lung Yu conceived of the presented idea. Chia-Yen Dai and Ming-Lung Yu wrote the manuscript in consultation with Wan-Long Chuang. All authors discussed the results and contributed to the final manuscript.

Reply to: “EASL recommendations on treatment of hepatitis C: Final update of the series – some issues”

The EASL Panel read with interest the Letter to the Editor by Dai et al. reporting their opinions on the final update of the EASL Recommendations on Treatment of Hepatitis C, published in the November 2020 issue of Journal of Hepatology.1 The Recommendations contain the responses to their comments, as well as the scientific evidence that supports them, as follows.

Regarding glecaprevir/pibrentasvir treatment duration in patients infected with genotype 3 with compensated cirrhosis: “A small number of patients infected with HCV genotype 3a with compensated (Child-Pugh A) cirrhosis have been included in clinical trials with the fixed-dose combination of glecaprevir and pibrentasvir [...] In the phase III EXPEDITION-8 trial, the efficacy of an 8-week treatment regimen in treatment-naïve patients with genotype 3a and cirrhosis is supported by the inclusion of only 63 patients, with 1 post-treatment relapse. In a real-world study including 11,101 adults treated with glecaprevir/
pibrentasvir for 8 or 12 weeks, the modified intent-to-treat SVR12 was smaller in the 679 patients infected with genotype 3 (95.8%) than in the 2,900 patients infected with genotypes 1, 2 and 4 (97.6% to 98.5%), but no predictive factors of virological failure have been identified. Thus, recommendations on treatment duration in patients infected with genotype 3a and compensated cirrhosis are based on moderate-quality evidence. Thus, the recommendation is: “Treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis should be treated with: […] (iii) the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks (A1). In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 weeks, but more data are needed to consolidate this recommendation (B1).”

As indicated in the EASL recommendations: “Simplified, genotyping/subtyping-free, pan-genotypic anti-HCV treatment must be used to improve access to HCV treatment and increase the global infection cure rates in any setting where genotype and subtype determination is not available, not affordable and/or would limit access to therapy (A1).” In such context, the collective benefit is preferred to an individual benefit, as far as the duration of glecaprevir/pibrentasvir administration or the addition of ribavirin to sofosbuvir/velpatasvir is concerned: “Lower SVR12 rates may be achieved in patients infected with HCV genotype 3 and compensated (Child-Pugh A) cirrhosis than in other patients, but efficacious retreatment strategies exist in individuals with virological failure.”

The issue of patients infected with genotype 3b, an HCV subtype inherently resistant to NS5A inhibitors relatively frequent in China and South-East Asia but rare in Europe, is discussed in another section of the EASL Recommendations: “In settings where sequence analysis of the NS5A region by means of population or deep sequencing is available and affordable, patients infected with subtypes 1l, 4r, 3b, 3g, 6u and 6v and patients infected with other infrequent subtypes harbouring ≥1 RAS(s) known to confer resistance to NS5A inhibitors should be considered for treatment with the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks, pending data with dual pangenotypic regimens (B2).” It is said elsewhere that: “Virological studies are required in countries in Africa, Asia and South America to determine the epidemiology, distribution and prevalence of HCV subtypes inherently resistant to NS5A inhibitors and thus to optimize treatment decisions without the need for individual HCV genotype and subtype determination.” This implies that the triple combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks may be indicated as first-line treatment in regions where HCV subtypes inherently resistant to dual NS5A inhibitor-containing regimens are highly prevalent and reliable HCV genotype and subtype determination is not available or affordable.

The EASL panel confirms that “Renal function, including creatinine and eGFR, should be ascertained (A1)” whenever possible, as part of regular medical care. Finally, “Given the high SVR12 rates expected with these regimens across all groups of patients if adherent, testing for SVR can be omitted (except in patients with high-risk behaviours and risk of reinfection who require SVR testing 12 weeks after the end of treatment and yearly thereafter whenever possible) (B1).”

Financial support
The authors received no financial support to produce this manuscript.

Reference

EASL Recommendations on Treatment of Hepatitis C Panel* 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) 22 807 03 60; fax: +41 (0) 22 328 07 24. E-mail address: easloffice@easloffice.eu

The role of the model for end-stage liver disease-sodium score and joint models for 90-day mortality prediction in patients with acute-on-chronic liver failure

To the Editor:

With great interest we read the article by Hernaez et al. The authors showed that the model for end-stage liver disease-sodium (MELD-Na) score underestimated the observed mortality risk in patients with acute-on-chronic liver failure (ACLF). As a result, patients with ACLF might be underserved in the MELD-Na-based allocation of donor livers. We agree with the authors that the MELD-Na score is not optimal for patients with ACLF, but we have a few additional comments on their paper.

First, the authors state that “it is unclear whether MELD-Na captures clinical severity” in patients with ACLF. Considering the available literature, it is clear that the disease course of ACLF is not captured by MELD-Na, especially for patients with ACLF-3. In their large UNOS analysis, Sundaram et al. already showed that ACLF death and waiting list removal rates are independent of MELD-Na score, as mortality rates were highest in MELD-Na <25 and ACLF-3 patients.