EASL recommendations on treatment of hepatitis C: Final update of the series – Some issues

To the Editor:
We read with great interest the final update of the EASL recommendations on the treatment of hepatitis C, which is one of the most important guidelines in the world.1 Having read the guidelines, we wanted to raise the following points:

For the treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis (naïve GT-3 CC), the recommendations mentioned that they should be treated with the fixed-dose combination of glecaprevir and pibrentasvir (glecaprevir/pibrentasvir) for 12 weeks, the fixed-dose combination of sofosbuvir and velpatasvir (sofosbuvir/velpatasvir) with weight-based ribavirin (1,000 or 1,200 mg in patients ≤75 kg or ≥75 kg, respectively) for 12 weeks, or the fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir for 12 weeks. For these naïve GT-3 CC patients, 8-week glecaprevir/pibrentasvir therapy is effective2 and has been approved by the U.S. FDA (September 2019) and European Commission (March 2020), as well as being recommended by the AASLD-IDSA guidance on hepatitis C published in 2019.3 Actually in the discussion about simplified, genotyping/subtyping-free, pan-genotypic (S-Gf-P) anti-HCV treatment, 8-week glecaprevir/pibrentasvir was recommended in any setting where genotype and subtype determination is not available, not affordable and/or would limit access to therapy, based on the determination of the presence or absence of cirrhosis by a non-invasive method.1 Since confirming the presence/absence of cirrhosis is mandatory in pretreatment evaluation for direct-acting antivirals (DAAs), 8-week glecaprevir/pibrentasvir can be recommended for treatment-naïve GT-3 CC patients. Notably, protease inhibitor-containing regimens are contraindicated not only in patients with currently decompensated (Child-Pugh B or C) cirrhosis but also in patients with compensated (Child-Pugh A) cirrhosis with previous episodes of decompensation.4 Thus, it is very important to carefully identify the history of decompensation in patients with compensated cirrhosis who are due to be treated with S-Gf-P regimens of glecaprevir/pibrentasvir. On the other hand, S-Gf-P regimens of 12-week sofosbuvir/velpatasvir are recommended for treatment-naïve and -experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis.5 However, sofosbuvir/
velpatasvir with weight-based ribavirin for 12 weeks has less favorable efficacy in genotype 3b patients (reported previously\(^1\)), as mentioned in the present EASL recommendations\(^2\) 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.\(^1,7\) 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.\(^1,3,6\)

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**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/