Clinical Trial Watch

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Clinical Trial Watch: Reports from the EASL International Liver Congress (ILC), Vienna, April 2015

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Viral hepatitis: Efficacy against hepatitis C is improving but resistance should not be neglected

The ILC brought very exciting news in the hepatitis C field, with relevant data on new treatment combinations and important studies on already approved treatment regimens. Probably, the most expected studies were those dealing with treatment of "difficult to cure populations", which are summarized in the following paragraphs.

Patients with decompensated cirrhosis

Patients with advanced liver disease, especially those with decompensated cirrhosis, have a poor prognosis and there is only limited experience with direct acting antivirals (DAAs) in this setting. Several clinical trials and studies in real life cohorts have addressed safety and efficacy issues in these patients.

The ALLY-1 study is a phase 3 trial that assessed the safety and efficacy of sofosbuvir (SOF), daclatasvir (DCV) and ribavirin (RBV) in patients with advanced cirrhosis and in post-liver transplant hepatitis C recurrence [1]. Sixty cirrhotic patients (20% Child-Pugh [CP]-A, 53% CP-B, and 27% CP-C) infected with genotypes 1 (G1) to 4 (75% G1) received 12 weeks of this oral regimen. The majority of patients had a MELD score between 10 and 15. The overall sustained virological response 12 weeks after treatment interruption (SVR12) was 83%, with excellent data in CP-A and B (92% and 94%, respectively), while efficacy dropped in patients with CP-C (56%), though the number of patients in this group was very small (n = 16). Non-response was explained by relapse in nine of the ten virological failures. No severe adverse events were attributed to study medication. A question that remains open is if extension to 24 weeks of therapy would reduce the rate of relapse in individuals with more advanced disease.

In the SOLAR-2 study [2], G1 or G4 decompensated cirrhotic patients (n = 160), both pre- and post-liver transplant (n = 53) were randomized to receive 12 or 24 weeks of ledipasvir (LDV), SOF and RBV. More than 50% of these patients had ascites, hepatic encephalopathy, and around 25% had a MELD score >15. Overall, this regimen resulted in high SVR12 rates (85–88%) independently of the treatment duration, both in the pre- and post-LT setting. It is important to notice that virological response was associated with improvements in MELD and CP scores from baseline, when assessed four weeks after treatment interruption. This was largely explained by a decrease in bilirubin and/or an increase in liver synthetic function (i.e. albumin). Indeed, 35% CP-B (n = 100) improved to CTP-A, and 48% of CP-C (n = 54) improved to CP-B. Despite this effect of viral clearance on liver function, improvements in portal pressure may take longer. Indeed, the effect of viral suppression on hepatic venous pressure gradient (HVPG) was characterized in 50 cirrhotic patients (CP-A: 18 and CP-B: 32) with portal hypertension (~85% HVPG >12 mmHg). Patients were randomized to receive 48 weeks of open-label SOF and RBV; a control group received the same therapy after a 24-weeks observation period [3]. When comparing baseline and end-of-treatment HVPG measurements in 37 cirrhotics with available paired assessments, HVPG decreased >20% in only 24% of individuals. The latter indicates that most patients would remain at risk of clinical decompensation, suggesting that the remodeling of fibrous septa and hepatic vascular changes in liver cirrhosis require a longer follow-up to improve or, that at some point, these changes are not reversible any more.

The safety and efficacy of a regimen not containing SOF to treat patients with advanced liver disease was presented at the ILC. The C-SALT trial [4] is a phase 2/3 study which assessed a 12-week all-oral combination of the NS3 protease inhibitor grazoprevir (GZR) and the NS5A inhibitor elbasvir (EBR). The study

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Abbreviations: SOF, Sofosbuvir; DCV, Daclatasvir; RBV, Ribavirin; CP, Child-Pugh; SVR, Sustained virologial response; HVPG, Hepatic venous pressure gradient; G, Genotype; LDV, Ledipasvir; GZR, grazoprevir; EBR, Elbasvir; SMV, Simeprevir; CKD, Chronic kidney disease; RAVs, Resistance associated variants; TACE, Transarterial chemoembolization; AAV2, Adeno-associated virus 2; CSC, Cancer stem cells; NSBBs, Non-selective beta blockers; ALD, Alcoholic liver disease; GWA, Genome-wide association; ARC, Alcohol related cirrhosis; MAIT, Mucosal Associated Invariant T-cells; NAFDL, Non-alcoholic fatty liver disease.

included 30 GT 1-infected patients with CP-B (CP-7 70%) cirrhosis and ten matched non-cirrhotic controls. Overall SVR12 was 90% (27/30), with a good safety profile.

Data on real life experience using SOF-containing regimens were also presented at the ILC. An update of SVR12 data coming from the TARGET cohort [5], which assessed the safety and efficacy of all-oral regimens in patients with a MELD score ⩾10, confirmed the results presented at the last AASLD [6,7]. SVR12 rates were around 75% in G1 patients treated with SOF and SMV ± RBV (with slightly higher efficacy in G1b), whereas SVR12 rates were significantly lower in G3 patients treated with SOF plus RBV (~40%). Foster *et al.* [8] presented an observational study conducted in 467 patients with decompensated cirrhosis infected with genotype 1 or 3 who underwent treatment with SOF plus LDV or DCV (with or without RBV). Around 65% of patients were CP-B with a mean MELD score of 12. Most G1 infected patients received SOF/LDV; most G3-infected patients received SOF/DCV (see below). SVR12 rates in G1 patients were very high, ranging from 81% to 86%. Four weeks after treatment interruption, MELD scores improved >2 points in 42% of patients but worsened in 11%. Preliminary analysis suggested that in older individuals (age >65) and in those with more advanced disease (albumin <35 g/L) treatment did not result in an improvement in liver function. Nevertheless, trying to identify those patients with decompensated cirrhosis who will benefit (or not) from viral clearance will require more studies and a longer follow-up after treatment interruption.

Additional studies including compensated and decompensated cirrhotic patients presented at the ILC are depicted in Table 1 [9–13].

G3-infected cirrhotic patients

Genotype 3 has become the most difficult to treat genotype, especially in treatment-experienced cirrhotic patients. Previous studies have already shown that in this setting, the combination of SOF and RBV, even when extended to 24 weeks, SOF/DCV (without RBV) or SOF/LDV and RBV for 12 weeks achieve only around 60–70% of SVR rates, which is clearly suboptimal in the current therapeutic scenario [14–16]. The BOSON study [17] is a multicentric, randomized, open-label clinical trial, assessing the efficacy of three different regimens: PegIFN, RBV and SOF for 12 weeks, and SOF plus RBV for 24 or 16 weeks. A total of 592 patients were included: G2 treatment-experienced with cirrhosis (n = 48) and G3 treatment naïve or experienced, with or without cirrhosis (n = 544). For G3-infected patients the highest SVR12 rates were obtained with PegIFN, RBV and SOF (93%), as compared with 84% and 71% with the 24- and 16-week SOF/RBV regimens, respectively. The results favoring a PegIFN-based regimen were even clearer in treatment-experienced cirrhotics, with an SVR12 of 86% in the PegIFN arm and only 77% and 47% in the 24- and 16-week SOF/RBV arms, respectively.

Regarding IFN-free therapy, SOF/DCV plus RBV for 12 weeks appeared to be a better choice than SOF/LDV plus RBV in G3 patients included in the English Extended Access Program [8]. Indeed, in this cohort which included mainly patients with decompensated cirrhosis, SVR12 rates were 70% in the 114 individuals who underwent SOF/DCV plus RBV compared to 59% in the 61 individuals who underwent SOF/LDV plus RBV. Based on data from the French compassionate use program [18], it seems that extending SOF plus DCV to 24 weeks might increase the

Table 1. SVR12 in patients with compensated and decompensated cirrhosis treated with different DAA-based regimen.

DAA-based regimen	N	Compensated/ decompensated	Genotype spectrum	Treatment duration (weeks)	SVR12
NS5B + NS5A ± RBV					
LDV/SOF or DCV ± RBV [8]	467	Decompensated	1, 3	12	59-70% in G3 81-86% in G1
LDV/SOF + RBV [2]	160	Decompensated	1, 4	12, 24	85-88%
DCV + SOF + RBV (preLT) [1]	60	Decompensated	1-6	12	83%
SOF + DCV ± RBV [18]	447	Mostly compensated	3	12, 24	76% and 88%, 12 and 24 weeks respectively
SOF + DCV ± RBV [9]	319	Mostly compensated	1	12 and 24	76% and 94% without RBV (12 and 24 wk) 100% and 98% with RBV (12 and 24 wk)[a]
SOF + DCV ± RBV [10]	107	Both	1-5	24	97-100%
NS5B + RBV					
SOF + RBV ± PegIFN *vs.* SOF + RBV [17][b]	171	Compensated	3	12, 16, 24	SOF + RBV ± PegIFN: 86-91% (12 wk) SOF + RBV: 47-57% (16 wk), 77-82% (24 wk)
NS5B + PI ± RBV					
SOF/SMV ± RBV [5]	136	Both	1	12, 24	72%
SOF + SMV [11]	103	Compensated	1	12	83%
SOF + SMV ± RBV [12]	144	Compensated	1	12	76%
PI + NS5A ± NS5B					
OBV/PTV/r [13]	42	Compensated	1b	12	90.5%
GZR + EBR ± RBV [30]	147	Compensated	1, 4, 6	12, 16	89-100%
GZR + EBR [29]	92	Compensated	1, 4, 6	12	97%
GZR + EBR + SOF [19]	41	Compensated	1	6, 8	G1: 80% and 94% (6 and 8 wk)

[a]SVR4.
[b]Only data for G3 patients are depicted.