Clinical Trial Watch

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Clinical trial watch: Reports from the AASLD Liver Meeting®, Boston, November 2014

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Summary

The late and fast developments in the field of viral hepatitis were highly expected in the 2014 AASLD Liver Meeting®. Several combinations using direct acting antivirals (DAAs) showed high rates of sustained virological response (~95%). Importantly, high cure rates were also demonstrated in patients with previous treatment failures, decompensated cirrhosis and hepatitis C recurrence after transplantation, making it clear that the interferon era is over (not so clear for ribavirin, which might still have a role in difficult-to-treat populations). Importantly, sustained virological response was associated with an improvement in liver function (MELD and Child-Pugh scores) in patients with advanced liver disease. In the field of liver cirrhosis, there were relevant data assessing the optimal empirical antibiotic therapy in patients with spontaneous bacterial peritonitis and high risk of resistant bacteria, as well as studies evaluating the role of terlipressin in type I hepatorenal syndrome and in septic shock. Regarding hepatic encephalopathy, two randomized trials suggest that the manipulation of the microbioma in patients with cirrhosis may have a role in the management of this complication. Some novel data on NASH support the beneficial effect of bariatric surgery (after failure of lifestyle intervention) in morbid obese patients with such diagnosis: clinical and histological improvements after surgery were evident in most patients with sufficient follow-up. A few controlled studies focused on the treatment of severe acute alcoholic hepatitis. Finally, several studies on hepatocellular carcinoma (HCC) were presented, covering topics such as ultrasound screening in cirrhosis, cryoablation treatment of early HCC and the relevance of downstaging in patients with HCC awaiting liver transplantation.

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Viral hepatitis: the interferon-free era is here to stay

Despite the outstanding development of new compounds to treat hepatitis C infection, there are still several unmet needs, including: 1) data from real-life cohorts evaluating the new antiviral combinations, 2) more efficacious therapies for difficult-to-treat patients, such as, non-responders to a previous course of therapy with a direct acting antiviral agent (DAA), genotype (G) 3-infected patients, decompensated cirrhotic patients and liver transplant recipients, and 3) new antiviral combinations allowing shorter treatment durations. In the last AASLD Liver Meeting®, several studies addressed these issues and brought new and exciting information to the field (Table 1).

Real-life cohorts

When antiviral therapies are used in clinical practice rates of sustained virological response (SVR) are usually lower as compared to the results obtained in registration trials. This is explained, in part, because difficult-to-treat populations are typically not included in these trials. In addition, side effects not observed in trials may appear after drugs have been registered. Therefore, results from these type of studies using new antiviral combinations are relevant.

Data from two large real-life cohorts evaluating sofosbuvir (SOF, a nucleotide NS5B inhibitor)-based therapies were presented at the meeting. Dieterich *et al.* reported data from 955 individuals included in the TRIO network [1]. Patients received a 12-week regimen either with SOF + pegylated interferon (PegIFN) + ribavirin (RBV) (n = 384), SOF + RBV (n = 227), or SOF + simeprevir (SMV, a second generation protease inhibitor, PI) ± RBV (n = 320). Thirty percent of the patients had cirrhosis and 43% were treatment-experienced (TE, including 20% of patients with history of failure to triple therapy with a PI). Intention-to-treat analysis showed SVR12 rates of 77% with SOF + PegIFN/RBV, 50% with SOF + RBV, and 82% with SOF + SMV ± RBV in G1-infected patients. Patients with cirrhosis had lower rates of SVR12 when treated with SOF + PegIFN/RBV (62% in cirrhotics *vs.* 76% in non-cirrhotics); the impact of cirrhosis on SVR12 rate appeared less important in patients receiving SOF + SMV (76% in cirrhotics *vs.* 87% in non-cirrhotics).

Table 1. Summary of clinical studies in patients with chronic hepatitis C presented at the AASLD Liver Meeting®.

Author (reference)	Type of study	Population	Cirrhosis n (%)	Treatment	SVR
Dieterich *et al.* [1]	Real-life	Chronic hepatitis C (n = 955) TN and TE	291 (30)	SOF + PEG + RBV 12 weeks (G1) SOF + RBV 12 weeks (G2) SOF + SMV ± RBV 12 weeks (G1)	77% 84% 82%
Jenssen *et al.* [2]	Real-life	Chronic hepatitis C (n = 2063) TN and TE	999 (49)	SOF + PEG + RBV 12 weeks (G1) SOF + RBV 12 weeks (G2) SOF + SMV ± RBV 12 weeks (G1)	85% 90% 89%
Bourliére *et al.* [3]	Trial	Chronic hepatitis C PI failures (n = 154)	154 (100)	SOF + LDV ± RBV 12 weeks SOF + LDV 24 weeks	96% 97%
Wyles *et al.* [4]	Trial	SOF failures (n = 51)	15 (29)	SOF + LDV + RBV 12 weeks	98%
Nelson *et al.* [5]	Trial	Genotype 3, TN and TE (n = 152)	32 (21)	SOF + DCV 12 weeks	TN 90% TE 86%
Bourliére *et al.* [6]	Trial	Cirrhotics included in phase 2 and 3 trials with SOF + LDV (n = 513)	513 (100)	SOF + LDV ± RBV 12 weeks SOF + LDV ± RBV 24 weeks	95% 98%
Flamm *et al.* [7]	Trial	Decompensated cirrhosis Genotype 1 or 4 (n = 108)	108 (100)	SOF + LDV + RBV 12 weeks SOF + LDV + RBV 24 weeks	87% 89%
Reddy *et al.* [8]	Trial	Liver transplant recipients (n = 223)	112 (50)	SOF + LDV + RBV 12 weeks SOF + LDV + RBV 24 weeks	92% 94%
Mantry *et al.* [9]	Trial	Liver transplant recipients (n = 34)	0	Paritaprevir/r + ombitasvir + dasabuvir + RBV 24 weeks	97%
Pungpapong *et al.* [10]	Real-life	Liver transplant recipients (n = 109)	28 (26)	SOF + SMV ± RBV 12 weeks	91%
Muir *et al.* [11]	Trial	Genotype 1, TN and TE (n = 202)	202 (100)	DCV + ASV + BCV 12 weeks DCV + ASV + BCV + RBV 12 weeks	TN 98%, TE 93% TN 93%, TE 87%
Poordad *et al.* [12]	Trial	Genotype 1, TN and TE (n = 415)	n.a.	DCV + ASV + BCV 12 weeks	TN 92%, TE 89%
Sulkowski *et al.* [13]	Trial	Genotype 1, TN (n = 94) HIV co-infection (n = 59)	n.a.	GZP + EBV ± RBV 12 weeks	93-98% 87-97%
Lawitz *et al.* [14]	Trial	Genotype 1, cirrhotics, TN, null responder with or without cirrhosis (n = 253)	170 (67)	GZP + EBV ± RBV 12 weeks GZP + EBV ± RBV 18 weeks	90-97% 94-100%
Lawitz *et al.* [15]	Trial	Genotype 1, TN (n = 102)	41 (40)	GZP + EBV + SOF 4 weeks GZP + EBV + SOF 6 weeks GZP + EBV + SOF 8 weeks	39% 80-87% 95%

SOF, sofosbuvir; PEG, pegylated interferon; RBV, Ribavirin; SMV, simeprevir; LDV, ledipasvir; DCV, daclatasvir; GZP, grazoprevir; EBV, elbasvir; TN, treatment naïve; TE, treatment-experienced; n.a., not available.

Importantly, tolerance to antiviral therapy was good and only 1.9% of the patients discontinued therapy due to adverse events.

The TARGET cohort, with more than 2000 patients enrolled, reported SVR4 in patients who received antiviral therapy with SOF + PegIFN/RBV, SOF + RBV, or SOF + SMV ± RBV [2]. Again, more than 50% of the patients were TE and 18% had failed a previous course of triple therapy with a PI. Forty-eight percent of the patients had cirrhosis and 43% of them had previous history of decompensation. SVR4 rates were 85% and 89% in patients receiving SOF + PegIFN/RBV and SOF + SMV ± RBV, respectively. In patients with decompensated cirrhosis the latter combination achieved SVR4 rates of 75%, but the degree of liver dysfunction was not reported for these individuals.

While awaiting the final results, preliminary data from these two study cohorts indicate that: 1) the efficacy of SOF + PegIFN/RBV in previously treated patients is similar to that predicted by the FDA (around 70%), 2) the combination of SOF + RBV in patients with G1-infection is suboptimal (SVR rate of 50%), 3) the combination of SOF + SMV ± RBV achieves high SVR rates, even in patients with cirrhosis or clinical decompensation, and 4) the use of ribavirin does not seem to significantly increase SVR rates, but in the absence of randomization strong recommendations cannot be given.

Non-responders to a previous therapy with a DAA

Bourliére *et al.* studied the safety and efficacy of ledipasvir (LDV, a NS5A inhibitor)/SOF in cirrhotic patients who had failed triple therapy with a PI [3]. Patients were randomized to receive placebo for 12 weeks followed by 12 weeks of LDV/SOF + RBV, or 24 weeks of LDV/SOF without RBV. The mean MELD score was 7 (range 6–16), 26% of the patients had esophageal varices and 17% had a platelet count $<100 \times 10^3/\mu l$, indicating portal hypertension. Despite being a difficult-to-treat population, SVR12 rates were 96% and 97% in the 12-week regimen with RBV and the 24-week regimen without RBV, respectively. Treatment was well tolerated and only one patient discontinued therapy because of sepsis during the placebo period.

The combination of LDV/SOF + RBV was also evaluated in the re-treatment of G1-infected patients who had failed previous therapy with a SOF-based regimen, either SOF in combination PegIFN + RBV (n = 25) or SOF + RBV (n = 21) [4]. SVR12 was 98%

and only one patient failed therapy due to relapse. Unexpectedly, this patient had been misclassified as G1a, but sequencing analysis at the time of relapse found that the patient was G3a.

Overall, these data suggest that, even in patients who have failed a previous therapy with a DAA, the combination of LDV/SOF plus RBV is able to achieve high SVR rates. Moreover, it appears that the addition of RBV is necessary to shorten treatment duration.

Genotype 3-infected patients

Due to the lower efficacy of current DAA against G3, patients infected with this genotype have become a difficult-to-treat population. The ALLY-3 study [5], was conducted to evaluate the combination of SOF and daclatasvir (DCV, a NS5A inhibitor) in G3-infected patients. In this trial, 101 treatment-naïve (TN) and 51 TE patients were enrolled. Twenty-two patients had cirrhosis. SVR12 was 90% and 86% in TN and TE patients, respectively. SVR12 was markedly lower in patients with cirrhosis (96% in non-cirrhotics *vs.* 63% in cirrhotics) independently of whether the patients had received a previous course of therapy or not. The main limitation of this trial was the lack of a comparison group with RBV or with longer duration of therapy (16 or 24 weeks).

It has previously been shown that TE patients with cirrhosis and G3 infection are a very difficult-to-treat population. Indeed, SVR12 with the combination of SOF + RBV was only 62% in G3 TE patients with cirrhosis [6]. Despite that both SOF and DCV have antiviral activity against G3, these data suggest that in patients with advanced liver fibrosis, a longer treatment duration, the use of RBV or even a third antiviral drug might be needed to increase efficacy.

Compensated and decompensated cirrhosis

Bourliére *et al.* [7] presented pooled data from patients with cirrhosis enrolled in phase 2 and 3 studies evaluating LDV/SOF. Overall, SVR12 rate was 96%. Virological failures were due to relapse (n = 18). A 12-week regimen with LDV/SOF without RBV achieved a slightly lower virological response (SVR12 of 92%) compared to a 12-week regimen with RBV (SVR12 of 95%) or a 24-week regimen with or without RBV (SVR12 of 100% and 98%, respectively). Patients with a platelet count $<75 \times 10^3/\mu l$, had lower chances of achieving SVR12 (84%). This combination was safe and well tolerated in patients with cirrhosis, but patients receiving RBV had higher rates of adverse events including anemia (hemoglobin <10 g/dl).

In decompensated cirrhotic patients, the SOLAR trial [8] evaluated treatment with LDV/SOF and RBV for 12 or 24 weeks in patients with G1 or G4 Child-Pugh B (7–9 points) or C (10–12 points) cirrhosis. The majority of the patients had a baseline MELD score between 10 and 20 points. SVR12 were 87% and 89% for 12 and 24-week treatment duration with no differences between Child-Pugh B or C patients. More importantly, antiviral therapy was associated with an improvement in MELD scores in most patients (60–79%), only 4 weeks after treatment finalization. Approximately one third of the individuals had serious adverse events (more frequently in patients receiving longer treatment duration), but most of them were not considered as related to antiviral therapy. Tolerance was good and only three patients discontinued therapy due to adverse events (sepsis, peritoneal hemorrhage and hepatic encephalopathy).

In summary, LDV/SOF achieves high SVR rates in patients with compensated and decompensated cirrhosis. A 12-week regimen with RBV appears to be the most cost/effective strategy. An important result from the SOLAR study in decompensated patients was the improvement in liver function. Pending validation with a longer follow-up and a higher number of patients, the data supports the indication of antiviral therapy in this population, even if they are not on a transplant waiting list. Since patients with Child-Pugh C >12 points were not included, the question remains as if viral clearance may or not have an effect in patients with very advanced cirrhosis.

Liver transplant recipients

Reddy *et al.* [9] presented the data evaluating LDV/SOF + RBV in patients with hepatitis C recurrence after liver transplantation (LT). This trial enrolled patients with all stages of fibrosis including F0–F3 (mild to moderate fibrosis) and cirrhosis (Child-Pugh A, B and C). Two hundred and twenty-three patients were randomized to receive LDV/SOF + RBV for 12 or 24 weeks. Most of the patients were male and were infected by G1a. Median time since transplantation ranged between 2.9 and 8.1 years. As expected, patients with preserved liver function achieved higher SVR12 rates (97% F0–F3 and 96% in Child-Pugh A patients) as compared to patients with decompensated cirrhosis (84% in Child-Pugh B and 64% in Child-Pugh C patients), without differences between 12-weeks or 24-weeks of therapy. The number of patients with Child-Pugh C cirrhosis enrolled in this trial is still very low and makes it difficult to draw any conclusions in this subpopulation. As usual, virological failures in this study were due to relapse (n = 8). Importantly, and as shown in immunocompetent patients, liver function improved in most of the individuals included in the trial (1 to 8 points decrease in MELD score). Twenty-five percent of the patients presented serious adverse events, but most of them were not considered as related to antiviral therapy. Adverse events were more common in patients with severe liver dysfunction or longer treatment duration. Mantry *et al.* [10] reported the results of the CORAL-I study aimed at evaluating the safety and the efficacy of paritaprevir/r, ombitasvir, dasabuvir and RBV in 34 liver transplant recipients with mild to moderate hepatitis C recurrence (F0–F2). Median time since transplantation was 39.5 months. Eighty-five percent of the patients were infected by G1a. SVR was achieved in 97% of the patients. The only patients who failed to respond to therapy had NS3, NS5A and NS5B resistance-associated variants at the time of relapse. Medication was well tolerated and only one patient discontinued therapy due to adverse events. Due to the presence of drug-drug interactions between ritonavir and immunosuppressive drugs, tacrolimus and cyclosporine, doses needed to be adjusted during therapy. Tacrolimus was reduced to 0.2 mg/72 h to 0.5 mg/week and cyclosporine was reduced to one fifth of the pre-treatment dose. Despite the adjustment on immunosuppression there were no episodes of rejection.

Real-life data from the three sites at the Mayo Clinic were reported by Pungpapong *et al.* [11]. One hundred and nine patients with hepatitis C recurrence after LT received antiviral therapy with SOF and SMV (with or without RBV). The majority of patients were infected with G1a, 29% had advanced fibrosis (F3–F4), and 11% had clinical or histological diagnosis of

cholestatic recurrence. SVR12 rate was 91% in 66 patients who had reached this time-point. Neither the use of RBV, the response to a previous treatment course of therapy, or the subtype of G1 were significantly associated with SVR12. On the contrary, SVR12 was significantly lower in patients with advanced fibrosis (F3–F4) as compared to patients with mild or moderate fibrosis (F0–F2, $p = 0.03$). Adverse events were mostly mild and unrelated to the study medication. However, one patient developed a drug-induced lung injury (confirmed by lung biopsy) and died of multi-organ failure.

New antiviral combinations

All-oral combination with asunaprevir (a NS3 inhibitor), DCV, and beclabuvir (a non-nucleotide NS5B inhibitor) was evaluated in G1-infected patients with [12] and without cirrhosis (n = 202 and n = 415, respectively) [13]. In patients without cirrhosis this combination obtained SVR12 rates of 92% and 89% in TN and TE patients, respectively. Thirty-four patients experienced virological failure, 13 were on-treatment failures, and the remaining 21 were relapses. Resistance-associated variants in NS3, NS5A and/or NS5B were commonly observed in G1a patients. Interestingly, G1b patients who failed to respond to therapy (n = 2) were subsequently classified as non-G1. In patients with cirrhosis, SVR12 was 93% and 98% in TN patients with and without RBV, respectively. The values for TE patients were 97% and 93%, with and without RBV. This combination was safe and well tolerated.

The final results of the C-WORHTY trial conducted in 471 patients with G1 chronic hepatitis C were presented [14,15]. In this phase 2 trial the combination of grazoprevir (MK-5172, a protease inhibitor) + elbasvir (MK-8742, a NS5A inhibitor) ± RBV was evaluated in 4 groups of patients: 94 TN non-cirrhotic patients, treated for 8 (only G1a) or 12 weeks; 59 HIV co-infected, non-cirrhotic patients, treated for 12 weeks; 123 TN, cirrhotic patients treated for 12 or 18 weeks; and 130 previous null responders to antiviral therapy with PegIFN/RBV, with or without cirrhosis, treated for 12 or 18 weeks. The combination of grazoprevir and elbasvir was highly effective in all treatment groups: 93%–98% in TN non-cirrhotic patients with 12 weeks of therapy, 87%–97% in HIV co-infected patients without cirrhosis, 90%–97% in TN cirrhotic patients, and 91%–100% in previous null responders with or without cirrhosis. The use of RBV or longer treatment duration did not have an impact on the chances of achieving SVR12. In G1a-infected patients receiving only 8 weeks of therapy with RBV, SVR12 was only 80%, indicating the need for longer treatment duration in these patients. Antiviral therapy with these two compounds was safe and well tolerated. Serious adverse events rate was 3% and only 3 patients discontinued therapy.

An interesting trial studied the possibility of ultra-short treatment durations with the combination of three highly potent DAAs [16]. Sixty-one TN, non-cirrhotic patients were randomized to receive grazoprevir + elbasvir + SOF for 4 or 6 weeks; and 41 TN patients with cirrhosis, were randomized to receive 6 or 8 weeks of the same combination. In non-cirrhotic patients, SVR4 rates were 38.7% and 86.7% for 4 and 6 weeks of therapy, respectively. In patients with cirrhosis SVR4 rates were 80% and 94.7% for 6 and 8 weeks of treatment, respectively. Virological failures were due to relapse, which were more frequently observed in G1a patients. At the time of the relapse 10 patients had NS5A RAVs (5 were also present at baseline). One patient had both, NS3 and NS5A RAVs. These data suggest that treatment regimens therapy in selected patients receiving a combination of highly potent drugs could be reduced in length, however going below 4–6 weeks has proven unsuccessful even in easy-to-treat individuals.

Hepatitis B

Despite being the major endpoint of antiviral therapy in patients with chronic hepatitis B, HBsAg loss is achieved in a minority of patients receiving antiviral treatment with nucleotide analogs or PegIFN. In this study, Marcellin *et al.* [17] aimed to investigate the rate of HBsAg loss at week 72 with a finite combination of tenofovir (TDF) + PegIFN. In this trial 740 patients were randomized to receive TDF + PegIFN for 48 weeks (Group 1), TDF + PegIFN for 16 weeks followed by monotherapy with TDF until completing 48 weeks (Group 2), indefinite treatment with TDF monotherapy (Group 3), or PegIFN for 48 weeks (Group 4). At weeks 72, HBsAg loss rate was significantly higher in Group 1 (9%) as compared to the other treatment groups (2.8%, 2%, and 0% for Groups 2, 3, and 4, respectively). It is important to note, though, that seven patients presented seroreversion (4 in Group 1 and 4 in Group 2). These data support the combination of TDF and PegIFN, but further studies are needed to confirm these results.

In summary, data presented showed an outstanding advance in the treatment of hepatitis C, especially in difficult-to-treat populations who are at high need of viral eradication: patients with cirrhosis and clinical decompensations, liver transplant recipients, patients with previous failure to a first generation protease inhibitor. However, the optimal duration of therapy and the use of RBV are still a matter of debate.

Complications of cirrhosis

Type I hepatorenal syndrome (HRS) is an uncommon but ominous complication in cirrhosis. The current standard therapy is based on the combination of vasoconstrictors plus albumin [18,19]. Terlipressin has been the vasoconstrictor most thoroughly assessed so far. In fact a recent meta-analysis shows that it is superior to placebo in the reversal of type I HRS [20]. However, terlipressin is still not approved by the FDA for this indication. Boyer *et al.* presented the initial results of a phase 3 multicenter, randomized trial comparing terlipressin + albumin *vs.* placebo + albumin in the treatment of HRS (the REVERSE study, [21]). The primary endpoint was "confirmed HRS reversal", defined as two serum creatinine values $\leqslant$1.5 mg/dl at least 48 h apart, on treatment. One hundred and ninety-six patients were enrolled. There were no significant differences in the rate of confirmed responses between the two groups (20% in terlipressin *vs.* 13% in placebo), or on 90-day survival. Terlipressin, however, induced a significantly greater decrease in creatinine than placebo. The same authors presented [22] the pooled data from this study and a previous one with similar design [23], showing a significant improvement in the rate of confirmed HRS reversal. Survival was significantly higher and the need for renal replacement therapy lower in patients achieving reversal.

Vasoconstrictors are also the mainstay of therapy in septic shock, but the optimal vasoconstrictor for patients with cirrhosis and septic shock remains unknown [24]. Choudhury *et al.* [25]

randomized 78 patients with cirrhosis and septic shock to continuous infusion of terlipressin or noradrenaline (in addition to standard medical care). The study was designed as a non-inferiority trial. The primary endpoint was maintenance of a MAP >65 mmHg at 6 h after the onset of infusion. The main cause of septic shock was spontaneous bacterial peritonitis (SBP). Terlipressin was not inferior to noradrenaline in achieving the primary endpoint. There were no differences in the overall survival.

Infections due to multiresistant bacteria are an increasing problem in cirrhosis, especially in those with nosocomial infections [26–28]. This issue was addressed in two randomized clinical trials evaluating the optimal empirical antibiotic therapy in patients with SBP at risk of infection by resistant bacteria. Piano *et al.* [29] conducted a randomized trial in 32 patients with cirrhosis comparing meropenem + daptomycin *vs.* ceftazidime in the empirical treatment of nosocomial SBP. The primary outcome was resolution of SBP at 7 days, and was achieved in 87% of the patients with meropenem + daptomycin and 25% with ceftazidime. Along the same lines, a second randomized trial presented by Jindal *et al.* [30], compared imipenem *vs.* cefepime in 175 patients with difficult-to-treat SBP (defined as nosocomial SBP, lack of initial response at 48 h to initial therapy or recurrent SBP). Resolution of SBP was achieved in 66% and 61% of the patients with imipenem and cefepime, respectively. The results of these two trials suggest that the most effective empirical treatment for patients with SBP at high risk of having resistant bacteria is likely the combination of a carbapenem with an agent active against resistant Gram positive cocci, though this might need adjustments to the local patterns of resistance.

Two randomized trials assessed the potential of probiotics for the management of hepatic encephalopathy (HE). Dhiman *et al.* [31] randomized 130 patients with cirrhosis who recovered from an episode of HE to receive VSL#3 or placebo (6 months treatment) for the prevention of HE recurrence. Probiotics achieved a non-significant reduction in the rate of recurrent HE as compared with placebo, but significantly decreased the rate of hospitalization, improved liver function and decreased serum pro-inflammatory markers in serum (TNFα, IL-1B, and IL-6). In another randomized trial Vlachogiannakos *et al.* [32] randomized 72 patients with cirrhosis diagnosed of minimal hepatic encephalopathy (MHE) to receive probiotics (*Lactobacillus plantarum* 299v) or placebo for 3 months. MHE was diagnosed by an abnormal NCT or abnormal brainstem auditory evoked potentials. Administration of the probiotic achieved reversal of MHE in a significantly greater proportion than placebo (57% *vs.* 7%). The rate of progression to overt HE was 0% and 17% respectively. These randomized trials suggest that the manipulation of the microbioma in patients with cirrhosis may have a role in the management of HE, though the effect of probiotics seems mild.

A decrease in portal pressure (evaluated by the hepatic venous pressure gradient or HVPG) is an excellent surrogate endpoint for improved outcomes in cirrhosis [33,34] and it has been used as a gold standard for proof of concept studies for new interventions. Two studies assessed the effects of diet and exercise on portal pressure in cirrhosis. Berzigotti *et al.* [35] evaluated the effects on portal pressure during a 16 week program of hypocaloric diet and supervised exercise in 50 obese cirrhotic patients (72% Child-Pugh A). The intervention reduced body weight and HVPG by a median of 5% and 11% respectively. Weight reduction was associated with the decrease in portal pressure, and 42% achieved a HVPG decrease $\geqslant$10%, showing the potential clinical impact of the intervention. The beneficial effects of diet and exercise might not be limited to obese patients [36]. In a small randomized control trial (n = 23) Macias-Rodriguez *et al.* [37] compared the effects on portal pressure of a 14-weeks physical exercise program combined with nutritional intervention *vs.* nutritional intervention alone in non-obese patients with cirrhosis, mostly Child-Pugh A. The exercise program was safe and associated with a significant reduction in HVPG as compared to the nutritional intervention group.

In summary, data from AASLD: 1) confirmed the beneficial effects of terlipressin in patients with cirrhosis and septic shock, 2) proved that antibiotic therapy for cirrhotic patients with nosocomial infection should include a carbapenem plus and anti-cocci agent, 3) evidenced that microbioma may play an important role in the development of HE, and 4) demonstrated that exercise and diet have a beneficial effect on portal pressure.

Non-alcoholic fatty liver disease and alcoholic liver disease

Non-alcoholic fatty liver disease (NAFLD) is currently one of the most common liver disorders both in the US and Europe [38,39]. It may progress to non-alcoholic steatohepatitis (NASH), which markedly increases the risk of cirrhosis and hepatocellular carcinoma (HCC) [40].

Novel approaches in diagnosis and treatment in NAFLD and non-alcoholic steatohepatitis (NASH)

Liver biopsy is often performed to confirm the diagnosis of NAFLD and diagnose NASH in high risk groups (e.g., patients with obesity, type-2 diabetes mellitus, dyslipidemia and metabolic syndrome). However, little is known about the long-term prognostic information that can be obtained from grading and staging the disease. In order to fill this gap, at this AASLD Liver Meeting®, Angulo *et al.* [41] presented the results of the PRELIHIN study, aimed to determine the long-term prognostic relevance of liver histological features in patients with NAFLD. In this prospective multicenter study, the authors analyzed the clinical value of histological features of 619 patients with confirmed NALFD, with a median follow-up of 12.6 years. They showed that age, diabetes and any stage of fibrosis at liver biopsy were independently associated with the primary outcome (e.g., death/LT). On the contrary, statin use was associated with a risk reduction (HR 0.32; $p = 0.005$). They also showed that an advanced fibrosis stage (F3 or F4 *vs.* F0; HR 14.2, $p < 0.001$ and 51.5, $p < 0.001$, respectively) was the only histological variable associated with liver-related events during follow-up. The authors concluded that fibrosis stage, but no other histological features or presence of NASH, is associated with important clinical outcomes on long-term follow-up of patients with NAFLD.

Given its impact on hard clinical outcomes, targeting fibrosis among patients with NAFLD/NASH is an important issue. One trial and one prospective cohort study including positive data of NAFLD/NASH and fibrosis, were presented in parallel sessions. In the first study, Harrison *et al.* [42] presented their results on safety and efficacy of GR-MD-02 (a galectin-3 inhibitor that has beneficial therapeutic effects in rodent models of NASH and toxin-induced cirrhosis) in patients with NASH and F3 fibrosis stage. In this early phase 1 study, 8 patients were randomized (3:1) to

receive 4 doses of either placebo or GR-MD-02 by intravenous infusion on days 0, 28, 35, and 42. Serum biomarkers of fibrosis (e.g., FibroTest® and Enhanced Liver Fibrosis (ELF) score) were assessed at day −1 and day 56. The authors report a good safety profile of the experimental drug, with no severe adverse events in both groups. A significant reduction of FibroTest® score (by a marked reduction in alpha-2-macroglobulin) was achieved in patients treated with GR-MD-02 *vs.* placebo (−27% *vs.* 3.5%; $p = 0.04$); however, no significant changes were found in ELF score. Finally, the authors inform that a clinical trial using a dose of 4 mg/kg of GR-MD-02, which will be followed by an 8 mg/kg dose cohort, is ongoing.

In the second study, Lassailly *et al.* [43] presented the results from one of the largest prospective cohort studies on the effects of bariatric surgery in morbid obese patients with histologically confirmed NASH. The study recruited 109 patients (89 with paired liver biopsies at 1 year of follow-up) over a time frame of 20 years. Anthropometric, biochemical and histological parameters were compared before and after one year from the surgical procedure. A significant improvement in anthropometric and biochemical parameters (e.g., BMI, insulin resistance index, ALT, GGT and HbA1c) were achieved. Importantly, NASH disappeared in 85% of cases and all histological features improved: steatosis (58.5 ± 22 to 17.2 ± 20%), ballooning (1.4 ± 0.5 to 0.3 ± 0.6), inflammation (1.3 ± 0.5 to 0.5 ± 0.6), NASH grading (1.5 ± 0.7 to 0.2 ± 0.6), NAS (4.9 ± 1 to 1.6 ± 1.5) and fibrosis (1.2 ± 1.1 to 0.9 ± 1.1) (for all: $p < 0.001$). The authors conclude that bariatric surgery might be used as an effective treatment after failure of lifestyle intervention in morbid obese patients with NASH.

Advances in the treatment of alcoholic liver disease: focus on severe alcoholic hepatitis

Alcoholic hepatitis (AH) is a type of acute-on-chronic liver failure and the most severe form of alcoholic liver disease [44]. In its severe form, AH carries a poor short-term prognosis. Although current guidelines recommend an adequate enteral nutrition support, in these patients the recommended protein-caloric intake is often difficult to achieve and effects of this maneuver compared with corticosteroids alone (the first line of therapy) has not showed any differences on short-term mortality [45]. However, the impact of enteral nutrition as an adjunctive therapy with corticosteroids is unknown. In this AASLD Liver Meeting® Moreno *et al.* [46] presented the results of a multicenter randomized controlled trial addressing this question. Two groups were included: 1) intensive enteral nutrition plus methylprednisolone (intensive group) and 2) conventional nutrition plus methylprednisolone (control group). In the intensive group, enteral nutrition was given using a feeding tube for 14 days and patients received Fresubin HP Energy® (1.5 kcal/ml, 7.5 g prot/100 ml): 1 L per day if body weight (BW) <60 kg, 1.5 L if BW between 60 and 90 kg, 2 L if BW >90 kg. The authors showed a significant improvement in 6-month survival (69.8 *vs.* 46.8%; $p = 0.015$, intensive *vs.* control group, respectively) when analyzing patients who received at least 80% of the planned kcal intake, defined by the protocol (per-protocol analysis). Importantly, on intention-to-treat analysis, the 6-month survival was not statistically different between the two groups: 55.9 *vs.* 47.0% ($p = 0.316$). Consequently, this trial fails to demonstrate the beneficial effects of intensive nutrition in severe AH. However, adequate nutritional support was associated with a better prognosis at 6-months.

In the clinical plenary session, Thursz *et al.* [47], presented the results of the STOPAH trial, a multicenter, double-blind, factorial (2 × 2) design which randomized 1093 patients with severe AH (discriminant function ⩾32) in 63 centers from the UK, to one of four groups of treatment: Group A: placebo/placebo, Group B: placebo/prednisolone, Group C: pentoxifylline/placebo and Group D: pentoxifylline/prednisolone. The trial aimed to provide sufficient power to determine whether either of the two interventions was effective in a non-biopsy proven cohort of AH. The primary endpoint (PE) was mortality at 28 days, with secondary endpoints (SE) being mortality at 90 days and 1 year. For pentoxifylline the odds ratio (OR) for PE was 1.07 (95% CI 0.77–1.49; $p = 0.68$) and for prednisolone the OR for PE was 0.72 (95% CI 0.52–1.01; $p = 0.056$). Importantly, when adjusting for baseline severity and prognostic factors (e.g., age, INR, urea, WBC, creatinine and HE) the OR in the prednisone treated group was 0.61 (95% CI 0.41–0.90; $p = 0.01$). No significant differences were found between treatment groups for SE. The authors concluded that prednisolone reduces the risk for 28-day mortality in ≈39% without impact beyond this time. Pentoxifylline treatment had no impact on PE or SE.

This meeting brought some important information regarding NAFLD and alcoholic liver disease: 1) advanced fibrosis at baseline biopsy is the major predictor of disease progression, death, or LT, 2) bariatric surgery has a beneficial impact on liver disease in patients with NAFLD, 3) adequate nutritional support improves outcome in patients with AH, and 4) pentoxifylline has no impact on survival in patients with AH.

Hepatocellular carcinoma: no big news but continuous improvement

The risk of developing HCC depends on the etiology of the liver disease. Among those, chronic hepatitis B virus infection is the world's leading cause of HCC [48]. It is crucial to identify patients at risk of HCC development to target surveillance population. Currently, there are several models but they require HBV DNA quantification, which may be a costly test in some areas of the world. Poh *et al.* [49] developed a score based on 673 chronic hepatitis B patients followed in Singapore for 10 years. Forty-three patients developed an HCC. The score is based on gender, age, cirrhosis and AFP level. The high risk group was defined as a score ⩾4.5. This score was validated on three independent cohorts totalizing 2586 patients. Nevertheless, the score took only into account baseline data, there was no time (survival) analysis and no treatment response was assessed.

Diabetes is another well recognized risk factor for HCC based on cohort or case control studies [50]. King *et al.* [51] reported an analysis coming from two prospective cohorts including lifestyle assessment. Over 30 years of follow-up, they identified 163 cases of HCC over 3,891,069 person/years. Diabetics had a higher risk of HCC (3.52, 95% CI: 2.44–5.08) compared to non-diabetics after adjustment for age, sex, BMI, aspirin use, smoking status and alcohol intake. The risk appeared to be independent of the sex, the duration of the diabetes, the BMI and the physical activity.

Diagnosis of HCC at an early stage is crucial for a successful treatment. For this purpose, ultrasound surveillance every 6 months is recommended by the international guidelines. Goldberg *et al.* [52] analyzed the database from a US commercial health insurance. Among 8916 cirrhotic patients followed during a median of 22.9 months, only 8.8% had a complete surveillance,

in 55.4% it was incomplete (ultrasound assessments missing) and 35.8% had no surveillance at all. Factors associated with incomplete surveillance were non-GI provider, non-PPO (Preferred Provider Organization) insurance, and elderly. Factors associated with "good" surveillance were a history of liver decompensation, a metabolic syndrome and a diagnosis of hepatitis B or C. The study stresses the lack of a correct information among HCC surveillance among physicians and the benefits of a specialized care (gastroenterologists and hepatologists) in cirrhotic patients.

When HCC is diagnosed at an early stage, radiofrequency ablation (RFA) provides very good results. New techniques for percutaneous tumor ablation have been developed during the last decade. Wang *et al.* [53] reported the results of a randomized control trial comparing RFA to cryoablation in 360 patients with 1 or 2 tumors, $\leqslant$4 cm. Local tumor recurrence was significantly more frequent after RFA compared to cryoablation at 1, 2, and 3 years but significantly more patients with two tumors were included in RFA group. There was no difference in terms of safety, overall survival, and tumor-free survival.

Liver resection (LR) is another treatment option for early HCC. Antiplatelet therapy has been recently shown to prevent hepatocarcinogenesis in animal models of HBV-induced HCC. Su *et al.* [54] presented a study that included 9461 patients with HBV-related HCC in Taiwan. Patients underwent LR between 1997 and 2011. After matching by sex, age and propensity score, 2210 patients were analyzed. Recurrence-free survival and overall survival were significantly better in patients who were under antiplatelet treatment, but the incidence of tumor recurrence was not reported. Moreover, statins were used more frequently in the antiplatelet group ($p = 0.054$). Overall, based on the data presented at the meeting, it is difficult to understand the real effect of antiplatelet therapy on prevention of tumor recurrence.

Test of time is one of the best tools for patient selection. In the LT setting, the waiting time is a "double-edged sword" for HCC patients, with the drop-out risk in one hand and a better candidate selection in the other. Mehta *et al.* [55] reported a series of 881 patients listed for LT for HCC in three centers with different waiting times. The 5-year post-LT patient survival was significantly better for patients with a waiting time $\geqslant$6 months ($p = 0.02$). However, a waiting time <6 months was not associated with a higher tumor recurrence in a multivariate analysis (making it difficult to interpret the waiting time effect). In the same area the crucial question of tumor downstaging feasibility is still under debate. A recent international consensus conference concluded that further evidences are needed. Mehta *et al.* [56] reported a multicenter experience on 187 patients fulfilling the downstaging criteria previously described, with at least 3 months of observation. The drop-out rate was 36%. The 5-year post-LT survival was 80% and the 5-year recurrence-free probability was 87% in transplant patients. For the whole study population (transplanted and not) a 5-year intent-to-treat survival of 56% was reached. Factors predicting tumor recurrence were pre-treatment AFP >500 and microvascular invasion. This study strongly supports that downstaging patients using stringent criteria is a safe procedure to allow some of them to access to LT.

No clinical trials on advanced stage HCC were released.

The AASLD Liver Meeting® showed us that: 1) diabetes, age and male gender are, as previously demonstrated, risk factors for the development of HCC, 2) percutaneous treatment with cryoablation is associated with lower rates of tumor recurrence but has no impact on tumor-free survival rate, 3) the beneficial effect of antiplatelet therapy on survival and tumor-free survival after LR for HCC needs further studies and 4) downstaging seems to be safe allowing more patients to get access to LT.

Disclosures

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References

[1] Dieterich D, Bacon B, Flamm S, Knowdley K, Milligan S, Tsai N, et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network: academic and community treatment of a real-world, heterogeneous population. Hepatology 2014;60:220A, [Abstract # 46].

[2] Jenssen D, O'Leary J, Pockros PJ, Sherman KE, Kwo P, Mailliard ME, et al. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. Hepatology 2014;60:219A, [Abstract # 45].

[3] Bourliere M, Bronowicki J, de Ledinghen V, Hezoce C, Zoulim F, Mathirin P, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. Hepatology 2014;60:1270A, [Abstract LB-6].

[4] Wyles D, Pockros PJ, Yang JC, Zhu Y, Pang PS, McHutchinson J, et al. Retreatment of patients who failed prior sofosbuvir-based regimens with all oral fixed-dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Hepatology 2014;60:317A, [Abstract # 235].

[5] Nelson D, Cooper J, Lalezari J, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week combination treatment with Daclatasvir and sofosbuvir in patients infected with HCV genotype 3: ALLY-3 phase 3 study. Hepatology 2014;60:1268A, [Abstract LB-3].

[6] Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993–2001.

[7] Bourliere M, Sulkowski M, Omata M, Zeuzem S, Feld J, Lawitz E, et al. An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin. Hepatology 2014;60:239A, [Abstract # 82].

[8] Flamm S, Everson G, Charlton M, Denning J, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective, multicenter study. Hepatology 2014;60:320A, [Abstract # 239].

[9] Reddy KR, Everson G, Flamm S, Denning J, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCD in patients with post-transplant recurrence: preliminary results of a prospective multicenter study. Hepatology 2014;60:200A, [Abstract # 8].

[10] Mantry PS, Kwo P, Coakley E, Te HS, Vargas HE, Brown RS, et al. High sustained virologic response rates in liver transplant recipients with recurrent HCV genotype 1 infection receiving ABT-450/r/ombitasvir+-dasabuvir plus ribavirin. Hepatology 2014;60:298A, [Abstract # 198].

[11] Pungpapong S, Werner KT, Aqel B, Leise MD, Murphy JL, Henry TM, et al. Multicenter experience using sofosbuvir and simeprevir with/without ribavirin to treat HCV genotype 1 after liver transplantation. Hepatology 2014;60:201A, [Abstract # 9].

[12] Muir AJ, Poordad F, Lalezari J, Everson G, Dore GJ, Kwo P, et al. All oral, fixed-dose combination therapy with Daclatasvir/Asunaprevir/Beclabuvir ± Ribavirin for chronic genotype 1 infection and compensated cirrhosis: UNITY-2 phase 3 SVR12 results. Hepatology 2014;60:1267A, [Abstract LB-2].

[13] Poordad F, Sievert W, Mollison L, Brau N, Levin JM, Sepe TE, et al. All oral, fixed-dose combination therapy with Daclatasvir/Asunaprevir/Beclabuvir for non-cirrhotic patients with chronic genotype 1 infection: UNITY-1 phase 3 SVR12 results. Hepatology 2014;60:1271A, [Abstract LB-7].

[14] Sulkowski M, Hezoce C, Gerstof J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of MK-5172 + MK-8742 ± ribavirin in HCV mono-infected and HIV/HCV co-infected treatment-naïve, non-cirrhotic patients with hepatitis C virus genotype 1 infection: the C-WORTHY study (Final results, Parts A and B). Hepatology 2014;60:318A, [Abstract # 236].

[15] Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null response: final

results of the C-WORTHY Study (Parts A and B). Hepatology 2014;60:296A, [Abstract # 196].
[16] Lawitz E, Poordad F, Gutierrez JA, Evans B, Hwang P, Robertson M, et al. C-SWIFT: MK-5172 + MK-8742 + Sofosbuvir in treatment-naive patients with hepatitis C virus genotype 1 infection, with and without cirrhosis, for durations of 4, 6, or 8 weeks. Hepatology 2014;60:1286A, [Abstract LB-33].
[17] Marcellin P, Ahn S, Ma X, Caruntu FA, Tak W, Elkashab M, et al. HBsAg loss with tenofovir disoproxil fumarate (TDF) plus peginterferon alfa-2a (PEG) in chronic hepatitis B (CHB): results of a global randomized controlled trial. Hepatology 2014;60:294A, [Abstract # 193].
[18] Angeli P, Sanyal A, Moller S, Alessandria C, Gadano A, Kim R, et al. Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: report from the International Club of Ascites. Liver Int 2013;33:16–23.
[19] Gines P. Hepatorenal syndrome, pharmacological therapy, and liver transplantation. Liver Transpl 2011;17:1244–1246.
[20] Sagi SV, Mittal S, Kasturi KS, Sood GK. Terlipressin therapy for reversal of type 1 hepatorenal syndrome: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol 2010;25:880–885.
[21] Boyer T, Sanyal A, Wong F, Frederick T, Lake J, O'Leary JG, et al. Initial report of a large, randomized, double blind, placebo-controlled, phase 3 trial of terlipressin plus albumin for the treatment of type 1hepatorenal syndrome (HRS-1): the REVERSE study. Hepatology 2014;60:255A, [Abstract # 114].
[22] Sanyal A, Boyer T, Frederick T, Regenstein F, Rossaro L, Araya V, et al. Reversal of hepatorenal syndrome type 1 (HRS-1) with terlipressin plus albumin versus placebo plus albumin – Not all responses are created equal – An analysis of the REVERSE and OT-0401 trials. Hepatology 2014;60:322A, [Abstract # 241].
[23] Sanyal AJ, Boyer T, Garcia-Tsao G, Regenstein F, Rossaro L, Appenrodt B, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. Gastroenterology 2008;134:1360–1368.
[24] Gines P, Fernandez J, Durand F, Saliba F. Management of critically-ill cirrhotic patients. J Hepatol 2012;56:S13–S24.
[25] Choudhury AK, Vashishtha C, Saini D, Kumar S, Sarin SK. A prospective open label randomized noninferiority trial to compare the efficacy and safety of monotherapy with noradrenaline and terlipressin in patients of cirrhosis with septic shock admitted to the Intensive care unit (NCT01836224). Hepatology 2014;60:254A, [Abstract # 113].
[26] Fernandez J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55:1551–1561.
[27] Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. Clin Gastroenterol Hepatol 2012;10:1291–1298.
[28] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–1324.
[29] Piano S, Salinas F, Morando F, Cavallin M, Rmano A, Rosi S, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis: results of a randomized controlled clinical trial. Hepatology 2014;60:57AA, [Abstract # 574].
[30] Jindal A, Sarin SK. A randomized trial of 'Imipenem versus Cefepime' in difficult to treat spontaneous bacterial peritonitis (SBP) and to evaluate the risk factors for treatment failure. Hepatology 2014;60:279A, [Abstract # 162].
[31] Dhiman RK, Rana BS, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Efficacy and safety of a probiotic preparation in the secondary prophylaxis of hepatic encephalopathy in cirrhotic patients: final results of a double blind, randomized, placebo controlled study. Hepatology 2014;60:278A, [Abstract # 159].
[32] Vlachogiannakos J, Vasianopoulou P, Viazis N, Chroni M, Voulgaris T, Ladas SD, et al. The role of probiotics in the treatment of minimal hepatic encephalopathy. A prospective, randomized, placebo-controlled, double-blind study. Hepatology 2014;60:376A, [Abstract # 353].
[33] Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902–908.
[34] Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. J Hepatol 2007;46:734–742.
[35] Berzigotti A, Albillos A, Villanueva C, Genesca J, Ardevol A, Augustin S, et al. Lifestyle intervention by a 16-week programme of supervised diet and physical exercise ameliorates portal hypertension in patients with cirrhosis and obesity: the SportDiet study. Hepatology 2014;60:253A, [Abstract # 110].
[36] Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:e1922.
[37] Macias-Rodriguez MA, Torre A, Ilarraza-Lo-meli H, Ruiz-Margain A, Garcia-Flores O, Duarte-Rojo A. Changes on hepatic venous pressure gradient induced by a physical exercise program in cirrhotic patients: a randomized open clinical trial. Hepatology 2014;60:246A, [Abstract # 96].
[38] Ratziu V, Bellentani S, Cortez-Pinto H, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 2010;53:372–384.
[39] Chalansani N, Younossi Z, Lavine J, Dielh A, Brunt E, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–1609.
[40] Yatsuli S, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. J Gastroenterol Hepatol 2009;24:248–254.
[41] Angulo P, Kleiner D, Dam-Larsen S, Adams L, Einar B, Charatcharoenwitthaya P, et al. The prognostic relevance of liver histology features in nonalcoholic fatty liver disease: the PRELHIN study. Hepatology 2014;60:226A, [Abstract # 59].
[42] Harrison S, Chalasani N, Lawitz E, Marri S, Noureddin M, Sanyal A. Early phase 1 clinical trial results of GR-MD-02, a galectin-3 inhibitor, in patients having non-alcoholic steatohepatitis (NASH) with advanced fibrosis. Hepatology 2014;60:225A, [Abstract # 57].
[43] Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Raverdy V, et al. Effects of bariatric surgery on severe liver injury in morbid obese patients with proven NASH: a prospective study. Hepatology 2014;60:305A, [Abstract # 213].
[44] Altamirano J, Bataller R. Alcoholic liver disease: pathogenesis and new targets for therapy. Nat Rev Gastroenterol Hepatol 2011;8:491–501.
[45] Cabré E, Rodríguez-Iglesias P, Caballería J, Quer J, Sánchez-Lombraña J, Parés A, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology 2000;32:36–42.
[46] Moreno C, Trepo E, Louvet A, Degré D, Bastens B, Hittelet A, et al. Impact of intensive enteral nutrition in association with corticosteroids in the treatment of severe alcoholic hepatitis: a multicenter randomized controlled trial. Hepatology 2014;60:269A, [Abstract # 141].
[47] Thursz M, Richardson P, Allison M, Austin A, Bowers M, Day C, et al. Steroids or pentoxifylline for alcoholic hepatitis: results of the STOPAH trial. Hepatology 2014;60:1267A, [Abstract LB-1].
[48] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
[49] Poh Z, Lin CY, Goh B, Chang J, Tan C, Shen L, et al. Real world risk score for hepatocellular carcinoma (RWS-HCC): development and external validation of a clinically practical score to identify low risk individuals. Hepatology 2014;60:280A, [Abstract # 164].
[50] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118–1127.
[51] King LY, Khalili H, Chung RT, Chan AT, Huang ES. Diabetes mellitus is associated with an increased risk of HCC in a large prospective cohort with long term follow-up. Hepatology 2014;60:281A, [Abstract # 165].
[52] Goldberg DS, Lewis JD, Valderama A, Kamalakar R, Babajanyan S, Sansgiry SS. Hepatocellular carcinoma (HCC) surveillance among cirrhotic patients with commercial health insurance: national rates and determinants of surveillance. Hepatology 2014;60:281A, [Abstract # 166].
[53] Wang C, Bai W, Dong Z, Lu Y, Zeng Z, Lou M, et al. A multicenter randomized control trial of percutaneous cryoablation versus radiofrequency ablation therapy in patients with hepatocellular carcinoma. Hepatology 2014;60:282A, [Abstract # 168].
[54] Su C, Lee P, Huo T, Huang Y, Lee K, Lin H, et al. Antiplatelet therapy is associated with better prognosis in patients with hepatitis B virus-related hepatocellular carcinoma after resection surgery. Hepatology 2014;60:198A, [Abstract # 4].
[55] Mehta N, Yao FY, Heimbach J, Harnois DM, Burns JM, Lee D, et al. Short waiting time predicts early recurrence of hepatocellular carcinoma after liver transplantation: a multicenter study supporting the "ablate and wait" principle. Hepatology 2014;60:446A, [Abstract # 504].
[56] Mehta N, Sarkar M, Guy J, Osorio RW, Frenette CT, Minteer WB, et al. Multicenter study of down-staging of hepatocellular carcinoma (HCC) to within Milan criteria before liver transplantation (LT). Hepatology 2014;60:253A, [Abstract # 111].