The 26th Conference of the Asian Pacific Association for the Study of the Liver (APASL 2017) was celebrated between February 15 and 19, 2017 at the Shanghai International Convention Center, Shanghai, China. The APASL 2017 Conference covered new developments, research updates and technological advancements in the field of liver diseases. Viral hepatitis treatment and epidemiology, as well as various scientific and clinical aspects of NAFLD and NASH were among the most relevant subjects of the meeting. In the case of viral hepatitis, the consolidation of the hepatitis C treatment revolution has led to the approval of direct acting antivirals (DAAs) in a large number of countries, the testing of new DAAs combinations, confirmatory studies in Asia and the use of these products in difficult to treat settings. In the field of Chronic Hepatitis B (CHB), the impact of long term treatments on preventing cirrhosis, hepatocellular carcinoma or other unfavorable events was one of the central areas. Nucleos(t)ide analogues (NUCs), the most used CHB treatment evidenced a poor efficacy in preventing disease progression compared to PegIFN in a large and long-lasting study. The understanding of bone- and kidney-related adverse reactions and the results of the study of irregular medication with NUCs as a detonator of acute on chronic liver failure (ACLF) in an important proportion of cases were important safety concerns discussed at APASL2017.

Keywords: APASL 2017, chronic hepatitis B, hepatitis C, therapy, nucleos(t)ide analogues, direct acting antivirals

26 Congreso de la Asociación Asiática del Pacífico para el Estudio del Hígado (APASL 2017). El 26 Congreso de la Asociación Asiática del Pacífico para el Estudio del Hígado (APASL 2017) se celebró entre los días 15 y 19 de febrero de 2017, en el Centro Internacional de Convenciones de Shanghai, China. El evento cubrió los nuevos desarrollos en el campo de las enfermedades hepáticas, el tratamiento y la epidemiología de las hepatitis virales, y los diversos aspectos científicos y clínicos de la enfermedad del hígado graso no alcohólico (NAFLD) y la estatohepatitis no alcohólica (NASH), entre otros temas. La consolidación de la revolución del tratamiento de la hepatitis C ha conducido a la aprobación de antivirales de acción directa (DAAs) en un gran número de países, la prueba de sus nuevas combinaciones, a estudios confirmatorios en Asia y al uso de estos productos en casos de difícil tratamiento. En la hepatitis B crónica (CHB), el impacto de los tratamientos a largo plazo sobre la prevención de la cirrosis, el carcinoma hepatocelular y otros eventos adversos fueron temas centrales. Los tratamientos con análogos de nucleósidos (NUCs), el más utilizado para la CHB, evidenciaron una pobre eficacia para prevenir la progresión de la enfermedad en comparación con el interferón pegulado (PegIFN) en gran estudio de larga duración. También se discutió sobre la seguridad de las terapias, en particular sobre la comprensión de las reacciones adversas relacionadas óseas y renales, y los resultados del estudio de la medicación irregular con NUCs como detonante de la insuficiencia hepática aguda crónica en una proporción importante de casos.

Palabras clave: APASL 2017, hepatitis B crónica, hepatitis C, terapia, análogos de nucleósidos, antivirales de acción directa

Introduction

The 26th Conference of the Asian Pacific Association for the Study of the Liver (APASL 2017) was celebrated between February 15 and 19, 2017 at the Shanghai International Convention Center, Shanghai, China. This Conference brought together physicians, clinicians, researchers, nurses, academics, residents and allied health professionals in hepatology and related fields.

The 2017 Hepatitis Report revealed that viral hepatitis is a major public health challenge, with 1.34 million deaths by 2015, comparable to tuberculosis, and higher than those caused by the human immunodeficiency virus (HIV). While mortality from HIV, tuberculosis, and malaria is now declining, mortality caused by viral hepatitis is on the rise [1]. On the side of non-infectious liver diseases, the interest in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have peaked as these are the most common chronic liver diseases in the West [2, 3].

APASL 2017 covered the new developments, research updates and technological advancements in the study of liver, including the following topics: viral hepatitis, acute liver failure, molecular and cellular biology, NAFLD, alcoholic liver disease, metabolic and genetic diseases, autoimmune hepatitis and cholestatic liver disease, hepatitis B drug induced liver disease (DILD), viral hepatitis, portal hypertension and cirrhosis - pathophysiology and clinical studies, liver fibrosis, liver cirrhosis (LC), hepatocellular carcinoma (HCC) and other liver cancers, liver transplantation, biliary tract disease and imagmg.

The present report highlights the presentations related to the consolidation of the direct acting antivirals (DAAs) revolution for the treatment of hepatitis C virus (HCV) infection; the chronic hepatitis B (CHB) approved therapies, the new serum markers under validation in the field of CHB management, the new developments in the CHB treatment, the relevant data on CHB epidemiology and the impact of irregular medication with nucleotide analogues (NUCs) in acute-on-chronic liver failure (ACLF) development. The present report will also summarize some of the pertinent studies in epidemiology of NAFLD, NASH, and non-invasive interventional medicine as well as currently accepted management recommendations.

Consolidation of the DAA revolution in HCV treatment

The revolution of chronic hepatitis C treatments is an unavoidable advance highlighted in the meetings of major Societies for the Study of the Liver through the last five years. At present, a large number of countries have adopted the use of DAAs as part of their Clinical Treatment Guidelines and show solid results in terms of safety and efficacy both in clinical trials and real life setting. New antivirals, combination of the established, as well as several generics have been evaluated in the last 2 years, especially in difficult to treat settings. Studies consolidating and reproducing the previous safety and efficacy results were also conducted in patients with Asian background. The first post marketing study carried out in Japan was presented at APASL 2017 meeting.

Efficacy of novel chronic hepatitis C therapies in difficult to treat patients

Fiona McPhee, from Bristol-Myers Squibb, presented the Impact of baseline NS5A polymer-phisms on sustained virological response rates to treatment with Daclatasvir (DCV) plus Sofosbuvir (SOF) with or without Ribavirin (RBV) in patients infected with HCV genotypes prevalent in Asia. Dr McPhee group carried out a retrospective sub-analysis of resistance associated substitutions (RAS) observed at baseline and virological failure time points in patients infected with GT-1b, 2, 3 and 6, who were treated with DCV + SOF ± RBV for 12, 16 or 24 weeks. High sustained virological response (SVR) rates, near 90-100 %, were observed after using DCV + SOF ± RBV in the difficult-to-treat patient populations infected with HCV genotypes and frequently observed in Asia. SVR rates were minimally impacted in the few patients with baseline RAS, irrespective of genotype. Emergent NS5A RAS and no NS5B RAS were observed in patients not achieving SVR. These results suggest that the combination of DCV+SOF ± RBV offers an effective treatment option in a wide range of patient populations [4].

The combination of Elbasvir (EBR) and Grazoprevir (GZR) was also evaluated in patients with chronic infection with HCV genotype GT-1b, the most common HCV genotype globally, accounting for the largest proportion of infections in Europe, Latin America, Russia, Turkey, and East Asia. The efficacy of 12 weeks of once-daily EBR 50 mg/GZR 100 mg (NS5A inhibitor/NS3/4 protease inhibitor) was high, comparable across subgroups, including those with cirrhosis, high baseline viral load, and prior treatment failures [5].

Safety and efficacy data in different population backgrounds

New studies presented in this meeting supported the safety of some combinations in Asian and non-Asian patients. An integrated subgroup analysis of different clinical trials demonstrated that the combination of Sofosbuvir and Velpatasvir (VEL) was highly effective in Asian patients with an overall SVR12 rate of 99 %. None of the Asian patients experienced virologic failure or premature discontinuation due to adverse events (AEs) [6]. Patients with mild and moderate renal impairment at baseline were also studied in a retrospective analysis, evidencing the safety profile of SOF-based therapies in these groups. Mean renal function (measured as estimated glomerular filtration rate) remained stable during and after treatment. Overall, in patients who did not receive RBV, there were no kidney-specific adverse events. The AE occurred more frequently in patients with mild or moderate renal impairment as compared to those with normal renal function [7].

The combination of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) was evaluated in terms of safety and efficacy in adults with chronic GT-1b HCV infection from Mainland China, Taiwan, and South Korea. The SVR12 was achieved by 99.5 % of HCV GT1b-infected Asian patients (Mainland China, 99 %; South Korea, 100 %; Taiwan,100 %) treated with OBV/PTV/r + DSV for 12 weeks. The regimen was well tolerated; mostly mild AEs were reported [8].

Treatment with the all-oral, fixed-dose combination of DCV 30 mg (pangenotypic NS5A inhibitor), asunaprevir (ASV) 200 mg (NS3/4 protease inhibitor) and beclabuvir 75 mg (non-nucleoside NS5B inhibitor) twice daily (DCV-TRIO) achieved a high rate of sustained virologic response at follow-up week 12 (SVR12; 96 % in both the overall population and patients with cirrhosis). Virologic clearance in patients infected with HCV may be associated with improvement in hepatic fibrosis and decreased risk of HCC. In this sense, the group of Akuta N., from Toranomon Hospital, Tokyo, presented results demonstrating that the treatment with DCV-TRIO improved measures of hepatic fibrosis, numerically greater in in the presence of cirrhosis, among Japanese patients. It is important to highlight that this work was conducted using four different tests to assess the level of fibrosis: Fibrotest, Fibroscan, Fib-4 and APRI [9].

Post marketing study

DCV combined with ASV was the first all-oral treatment to be approved in Japan for chronic hepatitis C virus (HCV) genotype 1b infection in patients with/without compensated cirrhosis. The interim report of a post-marketing survey of DCV + ASV in Japanese patients treated in the routine clinical setting was presented by a Japanese group from the Toranomon Hospital in Tokyo and was focused on safety. The survey aimed to register a total of 3000 HCV-infected patients, including 1000 patients with compensated acute-on-chronic liver failure (ACLF) development.


cirrhosis, between September 2014 and August 2015. All patients received oral DCV 60 mg once daily + ASV 100 mg twice daily for 24 weeks. Patient background, administration status, concomitant medication, and measures of safety and efficacy were recorded [10].

In the safety set, a total of 538 patients (24.85 %) experienced a total of 811 adverse drug reactions (ADRs). Hepatic function disorder occurred in 315 patients (14.55 %). Common ADRs were: abnormal hepatic function (n = 133; 6.14 %), increased eosinophil count (n = 67; 3.09 %), increased alanine aminotransferase (n = 63; 2.91 %), increased aspartate aminotransferase (n = 61; 2.82 %), liver disorder (n = 58; 2.68 %) and pyrexia (n = 53; 2.45 %). The rates of ADRs in patients with/without compensated cirrhosis were generally comparable. Serious ADRs were liver disorder (n = 5; 0.23 %), pyrexia (n = 4; 0.18 %); abnormal hepatic function (n = 3; 0.14 %) hepatic encephalopathy (n = 2; 0.09 %) jaundice (n = 2; 0.09 %). All serious ADRs resolved and all patients have recovered. No deaths were reported. The preliminary results of safety in this real-world study concluded that DCV + ASV therapy was generally well tolerated [10].

Studies related to treatment of CHB with approved therapies

Antiviral (NUCs) and immunomodulatory (IFN-based) therapies have been the state of the art for CHB treatment for several years. A large number of patients have been treated and at present the most relevant researchers in the field of hepatology are studying the impact of treatment in the incidence and risk prediction of HCC and in general in the long term efficacy variables (Table 1).

Pegylated interferon (PegIFN) therapy leads to a better long term clinical outcomes compared to entecavir (ETV)

A prospective cohort study report on the clinical long-term outcomes of PegIFN vs. ETV therapy in Chinese patients with HBeAg-positive CHB was presented by Shi-Ying Li and colleagues from the Key Laboratory of Molecular Biology for Infectious Diseases, Chongqing, China [11].

PegIFN and ETV are recommended products for first-line therapy of CHB infection by the EASL, AASLD, and APASL guidelines. However, their long-term effect, such as preventing LC and HCC, is controversial. The studies directly comparing the long-term outcomes of these two drugs are absent. From September 2001 to February 2016, a large, observational, open-label, prospective cohort study of HBeAg-positive CHB patients who received PegIFN or ETV therapy was carried out at the Second Affiliated Hospital of Chongqing Medical University. Cumulative incidences of unfavorable events (comprising LC and HCC) were calculated with respect to treatment type. Based on the REACH-B model, Chinese experts analyzed the incidence in these two groups, and compared the observed incidence of LC and HCC with the expected incidence in each group.

PegIFN treated patients showed a lower cumulative incidences of unfavorable events and cirrhosis than ETV treated ones. Univariate/multivariate exploration indicated that treatment types and platelet count were independently associated with the occurrence of unfavorable events in patients with CHB infection. Based on the REACH-B model, a lower observed cumulative incidence of HCC was observed in PegIFN treated patients than that of the predicted cases based on the REACH-B model. On the other hand, there was no significant difference of the cumulative HCC incidence between the observed and the predicted cases in the ETV experienced patients (P = 0.36, demonstrating a comparatively superior effect of PegIFN [11].

Concluding that treatment with PegIFN led to a lower incidence of unfavorable events including cirrhosis and HCC than ETV in patients with CHB is exceptionally relevant. The results presented by Shi-Ying Li and colleagues [11] are based in a prospective study during 15 years. The value of these results highlights the real contribution of the immunomodulatory therapies to the control of CHB disease progression. At the end of the day, limiting the evolution of the disease is the most sensitive and expected consequence of CHB treatment. These results, linked to the recently published data from Wranke and colleagues [20] showing the limited effect of antivirals in patients coinfected with Hepatitis Delta in contrast to PegIFN treatment may impact in the use of PegIFN as first line treatment for CHB therapy in a larger proportion of patients.

PegIFN impact on liver disease progression and serology

The HCC risk was assessed adapting the REACH-B score to the patients from the S-collate study. This study was presented by Dr Papatheodoridis and colleagues from Germany, Greece, China and Italy. The REACH-B score was developed in patients not receiving antiviral treatment. It was compared the result in S-Collate study using PegIFN Alfa-2a therapy with what would be predicted by the REACH-B score. The 4 years follow-up rendered an HCC incidence lower than predicted in the overall population except for patients with cirrhosis or transition to cirrhosis and non-Asian/Oriental patients, though the differences were not significant. A longer follow-up will confirm if these are robust trends [12], however the results per se are in line with the results presented by Shi-Ying Li and colleagues [11].

A sub-analysis of the same S-collate study explored the effectiveness of PegIFN therapy in HBeAg positive Chinese patients with CHB evaluated at 3 years post treatment [13]. The HBsAg clearance rate at 3 years post-treatment was 1 % in the ITT analysis and 3 % in the analysis of the available data, evidencing the limited effect of pegIFN on the HBsAg variable. HBeAg seroconversion (SC) rates were 26 % at the end of treatment (EOT) and 42 % at 3 years post-treatment. The combination of HBeAg SC and HBV DNA below 2000 IU/mL was achieved in 26 % (EOT) and 19 % at 3 years post-treatment. Only one HCC case was detected during the study in 396 HBeAg-positive Chinese patients. There were no deaths and no reports of decompensated liver disease, ascites, encephalopathy, or variceal bleeding in HBeAg-positive Chinese patients [13].
Aguilar Rubido JC, et al. Report

The effectiveness of pegIFN alfa-2a (40 kDa) therapy in HBeAg-negative Chinese patients with CHB at 3 years post-treatment as a sub-analysis of the S-collate study was also presented [14]. HBeAg-negative CHB is less common in China than in Europe, and few data are available on the outcome of treatment with PegIFN in the Chinese population. However, in recent years HBeAg-negative disease has an increased incidence in China. The objective of the observational S-collate study (NCT01011738) was to assess HBsAg clearance and other outcomes up to 3 years after stopping PegIFN treatment in patients with CHB. Response rates were calculated for the modified intention-to-treat (mITT) population (patients who received 1 or more doses of PegIFN) and for patients with available data at the time point of interest.

At 3 years post-treatment HBsAg clearance was documented in 7 % in the mITT population, and 13 % (9/69) in patients with data. The combination of HBV DNA < 2000 IU/mL and ALT normalization was achieved in 53 % (41/78) of patients at end of treatment and 32 % (20/62) at 3 years post-treatment (patients with data). There were no reports of decompensated liver disease, ascites, encephalopathy, or variceal bleeding. One case of HCC was detected and died during the study, while no other HBV-related deaths were reported. In summary, the results in Chinese HBeAg-negative patients from S-Collate are consistent with the results of large global phase 3 studies and show that HBsAg loss can be sustained for up to 3 years in some patients treated with PegIFN [14], although the response of this variable remains poor.

**Efficacy and safety of antivirals**

**Tenofovir disoproxil fumarate (TDF): 240 weeks on treatment follow-up in Chinese patients**

The efficacy and safety of 240 weeks of treatment with TDF for Chinese patients with CHB was presented by Jinlin Hou and colleagues [15]. This multicenter study involved 1118 Chinese subjects developing HBV-related ACLF, from January 2005 to December 2015, 761 had CHB and 357 with LC. In CHB patients, irregular medication accounted for the 8.94 % of cases and in LC patients for 19.33. In both cases the rate of improvement of the disease was the lowest; evidencing that the ACLF derived from irregular medication with NUCs is responsible for the most severe form of liver failure.

The study was developed in an interval of five years, patients with nucleoside analogues (ADV and TDF) showed significant decrease in glomerular filtrate rate compared to TDF. TDF induced a significantly higher proportion of patients with hypo-phosphatemia compared to ADV.

From 1118 Chinese subjects developing HBV-related ACLF from January 2005 to December 2015, 761 had CHB and 357 with LC. In CHB patients, irregular medication accounted for the 8.94 % of cases and in LC patients for 19.33. In both cases the rate of improvement of the disease was the lowest; evidencing that the ACLF derived from irregular medication with NUCs is responsible for the most severe form of liver failure. ADV: adeovir. ETV: entecavir. PegIFN: pegylated interferon. TAF: tenofovir alafenamide. TDF: Tenofovir disoproxil fumarate.

**Table. Selected chronic HBV approved therapies providing new efficacy data as presented in the 26th Conference of the Asian Pacific Association for the Study of the Liver (APASL 2017)**

<table>
<thead>
<tr>
<th>Product / Study focus</th>
<th>Results</th>
<th>Reference</th>
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<tbody>
<tr>
<td>PEG-IFN and ETV / a large observational, open-label, prospective cohort study of HBeAg-positive CHB patients who received PEG-IFN or ETV therapy: analysis of LC- and HCC-preventing capacity based on REACH B model (15 years period)</td>
<td>The analysis of a 15 years period (2001 to 2016) showed lower cumulative incidences of unfavorable events, HCC and LC in PEG-IFN than ETV treated patients. On the other hand, no significant difference in HCC cumulative incidence between the observed and the (REACH B) predicted cases in the ETV treated patients (P = 0.36)</td>
<td>11</td>
</tr>
<tr>
<td>PEG-IFN / The 4 years’ result of S-Collate Study (NCT01011738) was compared to what would be predicted by the REACH-B score</td>
<td>Lower HCC incidence after 4 years follow-up than predicted in the overall population except for patients with cirrhosis or transition to cirrhosis and non-Asian patients</td>
<td>12</td>
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<tr>
<td>PEG-IFN / Sub-analysis of the S-Collate Study explored the effectiveness of peginterferon therapy in HBeAg-pos / -neg Chinese patients at 3 years follow-up (3 years follow-up)</td>
<td>Lower HCC incidence after 4 years follow-up than predicted in the overall population except for patients with cirrhosis or transition to cirrhosis and non-Asian patients</td>
<td>13, 14</td>
</tr>
<tr>
<td>TDF / Efficacy and safety of 240 weeks of treatment with TDF for Chinese patients with chronic hepatitis B (CHB). Open-label phase with 497 patients (198 HBe-pos and 299 HBe-neg)</td>
<td>HBsAg loss at Week 240 (1) HBeAg-pos patient (0.2 %) HCC reported in 2 cases (0.8 %). HBs loss and serocon version was 46.1 and 34.8 % respectively. In summary, Chinese patients had a similar experience compared to patients from other countries</td>
<td>15</td>
</tr>
<tr>
<td>TDF / Analysis of HCC and deaths in cirrhotic (LC) patients who had received TDF 300 mg/day for at least 12 months vs. historical untreated patients. The 5-year cumulative probabilities of HCC, all-cause mortality and liver-related mortality were compared</td>
<td>The 5-year cumulative probability in TDF vs. control cohort was inferior for 13.5 % vs. 26.4 % for HCC (P = 0.001); 2.9 % vs. 23.3 % for liver-related mortality (P &lt; 0.001) and 2.9 % vs. 28.2 % for all-cause mortality (P &lt; 0.001), respectively. TDF treatment reduces the risks of HCC, liver-related and all-cause mortality in LC patients</td>
<td>16</td>
</tr>
<tr>
<td>TDF / Analysis of the association of TAF and TDF with bone mineral density (BMD) reduction. CHB patients from phase III trial (1298) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 96 weeks. Studies using Dual Energy X-ray Absorption scans</td>
<td>The changes in BMD over time and the percentage of patients &gt; 3 % BMD decline demonstrate significant safety benefits of TAF compared to TDF, most pronounced in high-risk populations from week 0 to 48 showed higher rates of &gt; 3 % BMD decline in hip and spine in high-risk groups (female gender, Asian race, older age (&gt; 50 years), and underlying renal disease (GFR &lt; 90 mL/min)) than in low-risk groups</td>
<td>17</td>
</tr>
<tr>
<td>TAF vs. TDF / Analysis of the association of TAF and TDF with bone mineral density (BMD) reduction. CHB patients from phase III trial (1298) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 96 weeks. Studies using Dual Energy X-ray Absorption scans</td>
<td>The study was developed in an interval of five years, patients with nucleoside analogues (ADV and TDF) showed significant decrease in glomerular filtration rate compared to TDF. TDF induced a significantly higher proportion of patients with hypo-phosphatemia compared to ADV</td>
<td>19</td>
</tr>
<tr>
<td>ADV and TDF vs. ETV / Analysis of the renal toxicity induced by Long-term nucleotide analogue treatment (ADV and TDF) compared to the nucleoside analogue (ETV) treatment in patients with CHB</td>
<td>From 1118 Chinese subjects developing HBV-related ACLF from January 2005 to December 2015, 761 had CHB and 357 with LC. In CHB patients, irregular medication accounted for the 8.94 % of cases and in LC patients for 19.33. In both cases the rate of improvement of the disease was the lowest; evidencing that the ACLF derived from irregular medication with NUCs is responsible for the most severe form of liver failure. ADV: adeovir. ETV: entecavir. PegIFN: pegylated interferon. TAF: tenofovir alafenamide. TDF: Tenofovir disoproxil fumarate.</td>
<td>14</td>
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<tr>
<td>All NUCs / Association of irregular medication with NUCs and the development of Acute on Chronic Liver Failure (ACLF). Analysis of the frequency and severity of ACLF resulting from irregular medication with NUCs in nine hospitals from China in a period of time from 2005 to 2015</td>
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<td>18</td>
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*The summary of the most relevant presentations at APASL 2017 demonstrated PEG-IFN superiority compared to nucleoside analogues (NUCs) in terms of hepatocellular carcinoma (HCC) and liver cirrhosis (LC) prevention after long term follow up, and also confirm their superiority in serum HBsAg loss or seroconversion. On the other hand, NUCs data at the meeting supported a significant impact in preventing complications and death in patients with liver cirrhosis, although NUCs should be administered regularly, without discontinuations. Irregular medication with NUCs account for the 20 % of all acute-on-chronic liver failure (ACLF) in cirrhotic patients and almost half of this proportion in CHB patients and in both scenarios, the ACLF induced by irregular medication with NUCs induce the most severe form of liver failure. ADV: adeovir. ETV: entecavir. PegIFN: pegylated interferon. TAF: tenofovir alafenamide. TDF: Tenofovir disoproxil fumarate.*
HBsAg loss at Week 240. A total of 19 out of 27 patients with paired biopsy (70.4%) had histological improvement. No resistance to TDF was detected throughout 240-week treatment. In 2 cases (0.8%) of HCC were reported at year 3 and 5. Creatinine increase was only detected in one patient that later resolved, evidencing that this was not a problem in this period of time for Chinese patients. Percentages of HBe loss and seroconversion in patients that received TDF for the complete 240 weeks period was 46.1 and 34.8% respectively. In summary, the experience of TDF use in Chinese patients was similar to patients from other countries [15].

TDF reduces HCC and deaths in CHB patients with LC
Antiviral therapies, such as lamivudine (LAM) and ETV, have shown to reduce HCC development and mortality in CHB patients with cirrhosis. TDF is a potent antiviral agent with no documented resistance to date, but its impact on clinical outcomes is unclear. Ken Liu from the Chinese University of Hong Kong, presented the results of TDF therapy on HCC and deaths [16].

Two cohorts of CHB cirrhotic patients were retrospectively studied. Cirrhosis was defined by liver histology, thrombocytopenia (< 150 x 10^9/L) or features of portal hypertension seen on imaging. TDF cohort included consecutive patients from two Asian centers who had received TDF 300 mg/day for at least 12 months. Control cohort included historical untreated patients who underwent routine clinical care. The 5-year cumulative probabilities of HCC, all-cause mortality and liver-related mortality were compared.

At the 5-year follow-up mark, there were 69 HCCs and 27 deaths of which 23 were liver-related. The 5-year cumulative probabilities in TDF vs. control cohort were inferior for 13.5% vs. 26.4% for HCC (P = 0.001); 29% vs. 33.5% for liver-related mortality (P < 0.001) and 29.2% vs. 28.2% for all-cause mortality (P < 0.001), respectively. On multivariate Cox regression model, TDF-treated patients had reduced risks of HCC, liver-related mortality and all-cause mortality at 5 years after adjustment for age, sex, MELD score and prior antiviral treatment experience. The authors concluded that TDF treatment reduced the risks of HCC, liver-related and all-cause mortality in CHB patients with cirrhosis in 5 years treatment period [16].

The effect of tenofovir on bone mineral density
Some doubts remain regarding the association of TDF with the appearance of osteoporosis. The data presented in relation with two Phase III studies involving TDF and Tenofovir Alafenamide (TAF), further clarified the effect of these antivirals on bone mineral density.

Patients from two phase III trial (1298) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 96 weeks. Dual energy X-ray absorptiometry (DXA) scans were performed throughout the first 48 weeks. Patients were evaluated for overall change from baseline and by proportion of patients with > 3% decline in bone mineral density (BMD). Changes in BMD were further assessed in patients at high risk for bone density loss, including female gender, Asian race, older age (> 50 years), and underlying renal disease (GFR < 90 mL/min). The mean (SD) % changes in hip BMD from baseline at week 48 for the TAF arm was –0.16 (2.24 %) and for the TDF arm was –1.86 % (2.45 %). For the spine, mean (SD) % change at week 48 was –0.57 % (2.91 %) in the TAF arm and –2.37 % (3.20 %) in the TDF arm. Subjects with > 3% decline in hip and spine BMD were significantly greater in TDF treated patients (27 and 38 %) compared to TAF treated patients (8 and 20 %). The percentage of patients with > 3% decline in hip and spine BMD was relatively consistent among TAF treated patients across baseline osteoporosis risk categories including female gender (8.6, 19.3%), Asian race (8.9, 19.5%), older age (8.8, 24.5%) and lower baseline creatinine clearance (8.6, 18.6%). In contrast, patients treated with TDF showed higher rates of > 3% BMD decline in hip and spine in high-risk groups than in low-risk groups [17].

The difference between TAF and TDF were more pronounced in patients with multiple risk factors, with TAF treated patients having 10% of patients experiencing > 3% decline in hip BMD regardless of number of risk factors. In contrast, 20% of TDF treated patients with 2 risk factors had a > 3% hip BMD decline while patients with 3 or 4 risk factors had 41 and 58% of patients with > 3% hip BMD decline at Week 48. A similar trend was seen with changes in spine BMD decline. The only baseline predictor consistent for having a < 3% hip and spine BMD decline at week 48 was treatment with TAF. The authors concluded that the changes in BMD over time and in proportion of patients with > 3% BMD decline in hip and spine demonstrate significant safety benefits of TAF compared to TDF. The safety benefits of TAF are most pronounced in high risk populations [17].

On the renal toxicity of nucleotide analogues
The long-term nucleotide analogue treatment (adefovir (ADV) and TDF) increase renal toxicities compared to the nucleoside analogue ETV treatment in patients with CHB, according to the group of Young Yoon Cho from the Department of Internal Medicine and Liver Research Institute at the Seoul National University College of Medicine. CHB patients treated with ADV based regimens are changing to TDF based treatments in Korea due to national reimbursement policies. Long-term renal effects of ADV experienced TDF treated patients was compared to ETV treated patients. In this retrospective single center study, authors selected 87 patients who were treated with ADV and subsequent TDF from June 2008 to Dec 2013. Patients were matched by treatment duration: ADV plus TDF (ADV + TDF group) with ETV treated patients, and treatment duration of TDF group with ETV treated patients. Nucleotide analogues showed significant decrease in GFR compared to ETV, and TDF showed significant hypophosphatemia development compared to ETV. A long term study needs to be performed in this population [18].

Switch from antivirals to immunomodulatory treatment
The NEW SWITCH study (NCT01464281) was reported by Dr Peng Hu, and colleagues from 24...
different affiliations in China. This multi-center, randomized study was conducted in HBeAg-positive CHB patients, who had received ADV, LAM or ETV for 1–3 years and achieved HBV DNA suppression (< 200 IU/ml) and HBeAg loss. Patients were randomized 1:1 to receive PegIFN for 48 weeks (arm A) or 96 weeks (arm B) with the first 12 weeks overlapping NUC therapy and followed-up for 48 weeks after treatment [21].

Among 153 patients randomized to arm A, 22 (14.4 %) achieved HBsAg loss at EOT, compared to 31 out of 150 (20.7 %) in arm B (P = 0.1742). The 96 weeks PegIFN treatment arm showed trends in better response in HBsAg loss at end of follow-up (EOF) and HBsAg serocconversion, HBeAg serocconversion and HBV DNA continued suppression at EOT and EOF. In patients treated with PegIFN alfa-2a for 96 weeks, HBsAg loss rate at EOT was 40 % (28/70) in patients with lower HBsAg level at baseline (< 1500 IU/ml) and 58.7 % (27/46) in patients with lower HBsAg level at baseline and week 24 (< 200 IU/ml). Similar populations in patients treated with PegIFN for 48 weeks (26.5 % (18/68) and 51.4 % (18/35)) were also found [21].

Patients involved in the NEW SWITCH study are selected from those eliminating HBeAg after antiviral treatment (10-20 % of those treated with antivirals), justifying the final impact on HBsAg serology.

**New developments in the field of treatment discontinuation for HBe-negative patients**

In the novel topic of treatment discontinuation, Dr. Papatheodoridis and colleagues [22] presented the impact of different definitions of relapse on the off-therapy remission rates in HBeAg-negative CHB patients who discontinue effective long-term treatment with NUCs. It is recognized that virological relapses are observed in the majority of chronic HBe-negative patients who discontinue NUCs, but whether all of them need retreatment was considered unclear. A total of 130 adult patients without cirrhosis before NUC onset (age: 57 ± 13 years, males: 69 %) were included. All patients had undetectable HBV DNA under NUCs for > 24 months and follow-up > 12 months after NUC cessation if they were not retreated. No patient had any co-infection, HCC, liver transplantation. After NUC cessation, patients were followed at least at months 1 and 3 and every 3 months thereafter.

Before NUC onset, median ALT was 105 IU/L and HBV DNA 498 000 IU/mL, while HBV genotype was B, C and D in 33, 8.5 and 58.5 % of patients, respectively. At NUC cessation, ETV was taken by 41 %, HBsAg 498 000 IU/mL, while HBV genotype was B and C in 32, 6.5 and 61 % of patients, respectively. A median duration of therapy was 55 months, on-NAs virological remission (38 months) and off-therapy follow-up until retreatment for retreated cases (15 months). No patient experienced liver decompensation or died. Retreatment according to practicing physicians’ decisions has been given in 40/130 (31 %) patients with a cumulative rate of 8, 16, 23, 31 and 38 % at 3, 6, 12, 18 and 24 months after NUC discontinuation. In multivariate Cox regression models, age, sex, genotype, pre-treatment ALT, HBV DNA levels were not associated with the probability of off-treatment relapse by any definition of retreatment, except for genotype D which was related with more frequent development of HBV DNA levels > 200 or > 2000 IU/mL (P < 0.020).

The authors concluded that the definition of relapse has a great impact on the rates of off-treatment remission and potentially on the probability of retreatment in HBe-negative patients. The majority of patients would have been retreated within 24 months if clinically significant relapse was considered as HBV DNA > 2000 IU/mL even with abnormal ALT, while retreatment would have been initiated in a minority of patients if more stringent criteria of relapse were adopted. Regardless of definition, off-treatment relapses cannot be easily predicted by patient characteristics [22]. A recent review and metaanalysis [23] that was part of the studies for the change of recommendation on the issue of discontinuation in Europe summarized the experiences from Hadziyannis [24], Höner [25] and Berg [26] demonstrating that discontinuation creates new immunological environment that may result even in HBsAg-related serological responses in a significant amount of patients (20 to 40 % depending on the study). On the other hand, the continuation under NUC treatment, or a quick restart of treatment do not favor any HBs loss or serocconversion after long term treatment as it has been well documented and also proven in the controlled study of Dr. Berg [26].

The anti-inflammatory effect of NUCs inhibit serological responses, and the discontinuation, if well managed under careful follow-up may open the door to a new scenario, in which the testing of therapeutic vaccines could have a new opportunity.

**New serum markers in the field of CHB management**

**The serum HBV RNA**

The elimination of covalently closed circular DNA (cccDNA) in hepatocytes remains a difficult target in CHB therapy; in addition, it is important to develop suitable markers that may predict the loss of cccDNA for the development of novel treatments or the optimization of the current ones. It has been reported that serum hepatitis B virus (HBV) RNA is encapsidated pregenomic RNA, directly transcribed from covalently-closed circular DNA (cccDNA). A study presented by Jie Wang, from China, assessed the relationship between serum HBV RNA and intrahepatic cccDNA activity in HBV-infected patients. Serum HBV RNA correlated with intrahepatic cccDNA in HBeAg-positive patients but not in HBeAg-negative patients. Serum HBV DNA also reflected cccDNA activity in HBeAg-positive patients, and HBV RNA plus DNA could reflect cccDNA activity better than either serum HBV RNA or DNA alone. Besides, serum HBV RNA could reflect the status of intrahepatic cccDNA in CHB patients after receiving a long-term NUCs-therapy. Therefore, the authors considered as reasonable to postulate that sustained loss of serum HBV RNA implicates the elimination or transcriptional silence of cccDNA [27].

**HBV core-related antigen**

Hepatitis B core-related antigen (HBcrAg) has been reported as an additional marker of HBV infection.
HBcAg assay was correlated with HBV DNA load in the sera and intrahepatic HBV cccDNA in tissues from HBV-related liver disease patients. Studying a group of CHB (n = 67), HBV-related HCC group (n = 160) and after heptectomy group (n = 14) it was found a strong correlation of HBcAg levels with serum HBV DNA both in the HBcAg-negative and HBcAg-positive groups respectively [28]. HBcAg was comparable with serum HBV DNA to reflect the virus replication in CHB, HCC and after heptectomy patients. The correlation between HBcAg and cccDNA was equivalent to the relationship of serum HBV DNA and cccDNA in HCC patients.

CHB treatment: new developments

Eclipsed by the spectacular results in the field of treatments for chronic hepatitis C, a wave of novel treatments approaches appear in the horizon of CHB therapy.

HBV core assembly modulator


Toll-like receptor 7 (TLR-7) agonist (RO6864018) in healthy subjects

A collaborative work among Roche Innovation Center & Pharma of Shanghai, and the General Hospital of Changi (Singapore) presented the new development of RO6864018, an oral double produg of the TLR-7-specific agonist, RO6871765, currently being evaluated in Phase II development as an immune modulator to treat patients with chronic HBV infection. A single ascending dose PK/PD ethnic bridging study generated safety, tolerability and PK/PD data in Asian and Caucasian healthy subjects [32]. No specific antiviral compounds were observed after 28 days of dosing. Changes in HBsAg levels were negligible, as expected from the short treatment duration. The largest mean HBV DNA reduction was observed with the 600 mg AL-3778/PegIFN combination (1.97 log IU/mL) which was greater than AL 3778 alone (1.72 log10) or PegIFN alone (1.06 log10). After 28 days’ treatment, mean HBV RNA (log10 copies/ml) changes from baseline were 0.00 in untreated, –0.73 in PegIFN treated, –0.82 in 600-mg BD AL-3778 treated and –1.5 in 600-mg BD AL-3778/PegIFN combination treated patients [29].

In summary, AL-3778 was well tolerated with main Grade 1 and 2, transient AEs. There was no life-threatening rash SAE related to the administration of the product. Dose-related HBV DNA reductions and HBV RNA reductions were observed, with evidence of additive antiviral effects in combination with PegIFN. Reduction of serum HBV RNA is consistent with the novel mechanism of action of AL3778, to disrupt efficient HBV RNA encapsidation [29].

HBsAg secretion inhibitors

The results of an ongoing randomized and controlled trial assessing the effect of Replicor family of nucleic acid polymers (NA) specifically REP 2139-Mg or REP 2165-Mg in combination with TDF and PegIFN in treatment naive patients with chronic HBsAg negative HBV infection was presented. Treatment was ongoing during APASL meeting. Forty patients should receive 26 weeks of lead-in TDF (300 mg) followed by randomization (1:1) into experimental and control groups. The experimental group should receive 48 weeks of TDF (same dose), PegIFN and REP 2139-Mg or REP 2165-Mg (1:1, 250 mg IV infusion weekly). Patients in the control group should receive 48 weeks of TDF + PegIFN and should cross to 48 weeks of experimental therapy in the absence of a 3 log drop in HBsAg after 24 weeks of PegIFN. Results were presented after twenty-nine patients have received > 12 weeks of treatment [30].

After TDF lead-in, most patients had serum HBV DNA < 10 IU/mL prior to PegIFN exposure. Triple combination therapy was well tolerated in all patients. One patient receiving REP 2165-Mg developed infusion reactions after the dose 20, otherwise no infusion reactions have been observed with either NAP. Serum HBsAg reductions, increases in serum anti-HBs or serum ALT/AST/GGT flares were negligible or absent during the TDF lead-in and in all but 2 patients in the control group to date. In patients having completed 12 weeks of NAP exposure, 9/9 receiving REP 2139-Mg and 6/9 patients receiving REP 2165-Mg have experienced > 1 log reductions in serum HBsAg. HBsAg reductions are > 3 log in 7/9 REP 2139 patients and 4/9 REP 2165 patients. Increases in serum anti-HBs are the most dramatic in these patients. NAP-mediated HBsAg reductions are accompanied by otherwise asymptomatic ALT/AST/GGT flares substantially greater than those in the control group. According to the authors, these data confirmed the tolerability and efficacy of REP 2139 and REP 2165 when used in combination with PegIFN and TDF in patients with HBcAg negative chronic HBV infection. Early clearance in serum HBsAg mediated by NAPs correlated with the onset of an intense transaminase flare and suggests NAP-mediated HBsAg clearance improves the efficacy of PegIFN in this patient population [30]. Previous results with other variants of the NAP family have produced encouraging results [31].

Multifunctional protein HBx is associated with HBV replication and carcinogenesis. Chemical compounds that suppress the function of HBx by binding to it could abrogate the mechanism of HBx-dependent HBV replication and carcinogenesis. Sayuri Morimoto from Tokyo University presented the in treatment naive HBcAg-positive chronic hepatitis B patients [Abstract]. Hepatol Int. 2017;11(Suppl 1):S7.


compounds’ effects on HBV replication as measured by the amount of HBV DNA in the culture medium using real-time PCR. In this experiment, HepG2.2.15.7 cells having stable HBV expression were used. Of the 1018 FDA-approved drugs in the library, 22 were found to bind to HBx, and 6 of them could strongly bind to HBx compared to others. Two compounds showed more than 50 % inhibition of the amount of HBV DNA. One of them showed more than 90 % inhibition, almost as good as 95 % inhibition of nucleoside analogue ETV. In conclusion, some FDA-approved drugs that bind to HBx were found to inhibit HBV DNA replication. These compounds, working in a different manner than ETV, could be an attractive option for the treatment of HBV-related diseases [33].

Pharmacology of HeberNasvac®, a novel therapeutic vaccine against CHB

After almost 20 years of research and development, Cuban National Regulatory Agency (CECMED) approved the Sanitary Registration of HeberNasvac®, a therapeutic vaccine to treat CHB patients. This novel product is administered by nasal and subcutaneous routes and encompasses the HBsAg and HBeAg purified as recombinant VLPs. The APASL presentation by Aguilar JC and colleagues compiled the data of non-clinical and clinical pharmacology of HeberNasvac® [34].

The studies in animal models were developed in Cuba, and also in collaboration with Pasteur Institute, Paris, France, and Ehime University in Matsuyama, Japan. Clinical trials were conducted in Cuba and also in Bangladesh. The preclinical immunogenicity studies, developed in normal Balb/c mice as well as in transfected and transgenic mice, supported the selection of the optimal formulation, the antigen doses and proportions, as well as the administration routes [35, 36]. HBsAg transgenic and adeno-associated virus-HBV transfected mice, in the background of humanized HLA, were used as models to evaluate the capacity of the nasal route of immunization to generate systemic and especially liver immune responses. HeberNasvac generated CD4(+) and CD8(+) T-cell responses and induced pro-inflammatory cytokines involved in viral control and disease resolution [36, 37]. According to the presenting author, the immunogenicity studies in the AAV model of CHB infection demonstrated the effect of nasal immunization in the homing of virus specific effector CD4 T cells to the liver in contrast to SC immunization.

Four clinical trials evaluated the safety and efficacy of HeberNasvac® as monotherapy, three of them in CHB patients and one in healthy volunteers. In general, HeberNasvac® vaccination was safe and induced strong antiviral and serological responses [38, 39]. The most important study of HeberNasvac® as monotherapy was the treatment controlled, and randomized phase III clinical trial conducted with the objective of evaluating the efficacy and safety of this product in CHB patients.

The phase III trial was designed for 160 CHB patients randomized in two groups (1:1). Both, HBeAg positive or negative patients with history of altered transaminases or moderate fibrosis/histological activity index were enrolled. In the first cycle the patients received five administrations of the formulation by IN route every two weeks. A second cycle of five administrations started one month after the first cycle. The second cycle encompassed 5 administrations of equal doses by the IN route and 5 subcutaneous injection given simultaneously. A dose of 100 µg of each antigen (100 µg of HBsAg and 100 µg of HBeAg) was used by each route [40].

In terms of safety, no serious or severe adverse events were detected after immunization by nasal and/or subcutaneous routes. The more frequent reactions were similar in nature for both products. The number of different AE, their frequency, intensity and duration were much more reduced in the group treated with HeberNasvac® compared to the AE induced by PegIFN.

In terms of efficacy, both the intention to treat and per protocol analysis showed a significantly higher proportion of vaccinated patients with HBV DNA below 250 copies/ml at the end of 24 weeks of treatment-free follow up compared to the proportion of patients in the same conditions 24 weeks after the end of PegIFN treatment. ALT values in HeberNasvac® immunized patients were characterized by a homogeneous, generalized and two to five times increase resembling immune activation followed by a viral load reduction. Such ALT increases were not clinically symptomatic and lead to a generalized normalization of ALT values at the end of HeberNasvac® treatment [40]. Serological evaluations evidenced a higher proportion of HBeAg negativization and seroconversion for HeberNasvac®-treated HBeAg positive patients at the end of follow-up.

ACLF and irregular medication with NUCs

ACLF is one of the most challenging health problems worldwide, characterized by its rapid progression and dramatically high mortality. In most Asian countries, hepatitis B causes 70-80 % of all etiologies of ACLF, so HBV-related ACLF is a serious public health. An important percentage and severity of HBV-related ACLF patients result from irregular medication of NUCs; this was the conclusion of the work presented by Ying Zheng and colleagues from different Chinese hospitals and medical universities [19].

The study focused on patients with HBV-related ACLF. From a total of 1118 subjects admitted to nine hospitals in Heilongjiang province from January 2005 to December 2015. 761 patients with CHB and 357 patients with HBV related LC were divided into six groups by different predisposing factors: irregular medication of nucleos(t)ide analogues (IMNA), HBV reactivation (HBVR), infection, drug, alcohol, others. The percentage and improvement rate of HBV-related ACLF induced by different predisposing factors were appraised by statistical analyses. In HBV-related ACLF patients with CHB, the percentage of IMNA was 8.94 %, HBV reactivation was 38.76 %, infection 9.33 %, drug 11.96 %, alcohol 8.54 and others 22.47 %. The improvement rate of IMNA was only 50.00 %, HBVR 64.75 %, infection 57.75 %, drug 58.24 %, alcohol 56.92 % and others 65.50 %. Multiple-factor analysis shows IMNA, hepatic encephalopathy, hepatorenal syndrome were
independent risk factors. In HBV-related ACLF patients with LC, the percentage of IMNA was 19.33, HBV reactivation 31.37, infection 5.32, drug 11.48, alcohol 7.00 % and others 25.49. The improvement rate of IMNA was 37.68 %, but after HBV reactivation was 56.25 %, infection 63.16 %, drug 48.78 %, alcohol 48.00 % and others 52.75 %. Multiple-factor analysis shows IMNA, infection, hepatic encephalopathy, hepatorenal syndrome are independent risk factors [19].

In summary, authors concluded that the percentage of irregular medication of NUCs induced HBV-related ACLF from nine hospitals was almost 20 % for LC patients and approximately the half in CHB patients, and the severity of the liver failure was the worse compared to other etiological factors. Authors recommend paying more attention to the treatment with NUCs because it may exacerbate the disease and even develop HBV-related ACLF in an important proportion of patients if it’s not correctly used [19].

NAFLD

The APASL meeting hosted many presentations that covered various scientific and clinical aspects of NAFLD. As usual to many disease management, outlining the underlying patient demographic at risk becomes vital in screening, management and follow-up of NAFLD with special consideration to the limited resources currently available for care. NAFLD is characterised by excessive hepatic fat accumulation, correlated with insulin resistance (IR), and defined by the presence of steatosis in > 5 % of hepatocytes per histological assessment [41]. The NAFLD spectrum varies from simple hepatic steatosis (SHS) or NAFLD to SHS plus a characteristic pattern of steatohepatitis (NASH), to steatosis or steatohepatitis associated with fibrosis, LC and HCC.

Multiple studies were presented during the 26th APASL meeting aimed at assessing the at-risk population around the world and application of non-invasive interventional diagnostic tools. Studies in Thailand, China, and Canada among many others attempted to identify underlying population at risk as well as effect of co-morbid liver diseases in disease progression, and severity.

NAFLD prevalence in asymptomatic population

Dr Teetarom and colleagues from Thailand presented a prospective study consisting of 871 patients that aimed to assess NAFLD prevalence in an asymptomatic population with low risk of alcoholic liver disease, CHB and CHC between Mar 2013 and Sep 2016. With a mean age of 56 ± 10 years and 70 % female sex, the prevalence of NAFLD was 61 % and severe steatosis was 17.2 %. Meanwhile, 41 % of the participants with body mass index (BMI) of 23 kg/m2 and normal waist circumference had NAFLD. They reported 32 % control where the controlled attenuation parameter (CAP) was 185 dB/m and mean liver stiffness was 4.1 kPa. They further went on to explain that the degree of moderate-to-severe steatois was significantly associated with diabetes mellitus (Odd ratio, OR 1.2), dyslipidemia (OR 1.1) and higher BMI (OR 1.06). The significant liver fibrosis, Liver stiffness (LS) higher than 8.0 kPa was 9 % and it was independently associated with higher BMI (OR 1.55). They concluded that in their patient population NAFLD prevalence was 61 % with 9 % significant liver fibrosis [42].

Metabolic syndrome in patients with CHB and co-morbid NAFLD

Another study originating out of China and presented by Dr Jiangao Fan assessed prevalence of metabolic syndrome in patients with CHB and co-morbid NAFLD [43]. The authors prospectively followed 1326 patients who had biopsy-proven CHB (n = 721), NAFLD (n = 176), CHB/NAFLD (n = 429) for a period of 1 to 15 years. They discovered that rate of metabolic syndrome was significantly higher in CHB/NAFLD compared with CHB alone. Furthermore, CHB Patients with comorbid NAFLD had higher risk of progression to HCC and experiencing liver-related death than patients with only CHB. In the NAFLD/CHB versus CHB group; respectively, prevalence of co-morbidities was: hypertension (9.4 %, 3.2 %), obesity (9.3 %, 0.8 %), diabetes mellitus (13.2 %, 4.2 %), and hyperlipidemia (12.4 %, 2.8 %).

Several presentations studied disease etiology and patient demographics, all pointing to the importance of screening high risk patients especially those with Diabetes Mellitus with fasting or random blood glucose or a standard 75g OGTT irrespective to liver enzymes. Data also suggests that all NAFLD patients had an increased risk of HCC and thus should be closely monitored.

Translant Elastography vs. Biopsy: is there a winner?

The questions of liver biopsy accuracy rate as well as it’s “golden test” title was put to the test by Canadian authors Boctor K. et al. [44, 45] who assessed comparatively the use of transient elastography to traditional liver biopsies in patients with biopsy proven NASH patients. In two separate studies the authors evaluated patient demographics, fibrosis staging, and the breakdown of NAS score comparatively to liver stiffness (LS) and CAP.

The first study consisted of 76 Canadian patients with NAS of 2 or greater, and identified the main reason for a specialty referral to be accidental finding of ALT elevation of annual examination. Dr Boctor et al. reported a mean age of 48 and 52 for males and females; respectively. Their study population had average LS of 14.6 kPa, and upon further break down, the NAFLD activity score was found to correlate to LS with a p-value of 0.021; however, a major discrepancy was visible when groups were broken down by transient elastography and liver biopsy fibrosis staging. They concluded in their first study that the strong correlation between NAS and LS proves the strength of transient elastography as a monitoring tool for NASH [44].

In the second study the authors assessed similar demographics as in the first one, in a separate cohort consisting of 75 NASH patients; however, they specifically focused on the use of CAP and compared it to NAS score and its components (Steatosis, Ballooning, and inflammation). They reported a mean age of 52.3, 41. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388-402.

cohort LS of 13.1 kPa and mean CAP of 328 dB/m. Their study findings suggested that strongly correlated to fibrosis ($P = 0.021$) however poorly correlated to steatosis ($P = 0.20$), ballooning, and inflammation on biopsy [45].

Through their use of evidence-based medicine, the most recent guidelines for NAFLD management considers that the diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption higher than 30 g for men and 20 g for women. Patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors. The definitive diagnosis of NASH requires a liver biopsy (Figure). Patients with Type 2 Diabetes Mellitus should be screened for NAFLD. The steatosis should always be documented whenever NAFLD is suspected as it is also predictive of future development of type 2 Diabetes Mellitus, cardiovascular events and arterial hypertension. In general these aspects were also confirmed at the APASL 2017 meeting.

**Concluding remarks**

The APASL2017 conference was a very well organized event with several novel presentations. As usual, since the last five years, several presentations were focused in the successful advances of HCV DAAs treatments. The evaluation of DAAs efficacy in patients from difficult to treat settings, as well as the first results of DAAs post-marketing studies in Japan, were the most attractive presentations in the HCV field.

Regarding CHB therapies, a large study, conducted through a long period of time (15 years) confirmed the effect of PegIFN in preventing HCC and LC development, while a similar effect was not demonstrated in the case of patients treated with NUCs (ETV). Several studies also confirmed the capacity of PegIFN to induce a modest but sustained serum HBsAg loss or seroconversion while NUC presented results confirmed the lack of effect on these serological variables. In favor of NUCs, data presented at APASL meeting supported their significant impact in preventing complications and death in the set of patients with LC when compared to historical control cohort.

Caution was requested to patients and doctors participating in the APASL Conference to avoid the irregular medication with antivirals, based in the fact that this misapplication is responsible of approximately the 20 % of all ACLF in cirrhotic patients and almost 10 % of CHB related ACLF. In both scenarios (LC and CHB patients), the liver failure caused by irregular medication with NUCs induced the most severe form of liver failure compared to other etiological causes, with the lowest proportion of patients improving after this serious event.

In developing and underdeveloped countries, where the CHB disease is more prevalent and governments are unable to provide CHB treatments, informative campaigns should be reinforced in support of regular medication with NUCs, otherwise the pharmacological and epidemiological impact of these products may be lost due to product misuse. The WHO target of controlling the increasing mortality of viral hepatitis found in the last decade may be at risk.

The Sanitary Registration granted to HeberNasvac®, the first therapeutic vaccine approved for the treatment of CHB (or any other chronic infectious disease), was announced during the APASL Conference. HeberNasvac® represents a finite, safe and effective alternative for the treatment of CHB patients and it was registered by the first time in its country of origin (Cuba) where it is being introduced in a large number of HBsAg-positive patients. The registration was granted based in the significant superiority of HeberNasvac® monotherapy in terms of safety and efficacy variables compared to PegIFN treatment.

The introduction of HeberNasvac® in CHB patients should be carefully followed, supported and assessed by WHO. This product could represent a valuable tool to accomplish WHO objective of eliminating viral hepatitis as a health problem by 2030, as proposed in the Hepatitis Global Report 2017 [1]. Poor countries and developing nations from BRICS cannot escape from the misuse of current antiviral treatments, producing the most severe form of ACLF and responsible of the 10 and 20 % of such liver failures in CHB and cirrhotic patients, respectively. In the countries where quasi-external therapies cannot be provided to patients in order to ensure their regular medication with NUCs, the approval of a novel, finite and effective treatment constitutes promising news.

**Acknowledgements**

We appreciate the critical review and useful discussions on the manuscript by Dr Eduardo Penton Arias, from the Vaccine Division, Center for Genetic Engineering and Biotechnology, Cuba.

