The International Liver Congress, April 13-17th, 2016, Barcelona, Spain

REPORT

Julio C Aguilar Rubido

Vaccine Department, Direction of Biomedical Research,
Center for Genetic Engineering and Biotechnology, CIGB
Ave. 31 e/ 158 y 190, Cubanacán, Playa, CP 11600, La Habana, Cuba
julio.aguilar@cigb.edu.cu

ABSTRACT

IThis report highlights the recent discoveries presented at the 2016 Annual Meeting of the European Association for the Study of the Liver (EASL), called the International Liver Congress (ILC), which was held in Barcelona, Spain, from April 13th to 17th. Major topics were: viral hepatitis; cirrhosis; immunology & inflammation; transplantation; tumours; fatty liver disease; drug induced diseases; diagnostics; molecular and cellular biology; paediatric liver diseases; clinical trials; autoimmune diseases; fibrosis markers and public health. The most relevant findings regarding the new products for the treatment of chronic hepatitis B, and also new developments in hepatitis C and D are discussed.

Keywords: International Liver Congress 2016, EASL, chronic hepatitis B, hepatitis therapy, therapeutic safety

Biotecnología Aplicada 2016;33:2501-2505

RESUMEN

Congreso Internacional del Hígado 2016, abril 13-17, 2016, Barcelona, España. En este reporte se destacan los más recientes descubrimientos presentados en la Reunión Anual de la Asociación Europea para el Estudio del Hígado (EASL), llamada Congreso Internacional del Hígado (ILC), celebrado en Barcelona, España, del 13 al 17 de abril. Sus temas principales fueron: hepatitis viral; cirrosis; inmunología e inflamación; trasplante; tumores; hígado graso; enfermedad inducida por fármacos; diagnóstico; biología molecular y celular; enfermedad hepática pediátrica; ensayos clínicos; enfermedades autoinmunes; marcadores de fibrosis y salud pública. Se discuten los hallazgos más relevantes acerca de los nuevos productos para el tratamiento de la hepatitis B crónica, y los desarrollos mostrados sobre las hepatitis C y D.

Palabras clave: Congreso Internacional del Hígado 2012, EASL, hepatitis B crónica, terapia contra la hepatitis, seguridad de la terapia

*I*ntroduction

The 2016 version of the Annual Meeting of the European Association for the Study of the Liver (EASL) called the International Liver Congress (ILC), took place in Barcelona, from April 13th to 17th. Among the biggest meetings in the World, the ILC gathered thousands of participants: hepatologists, gastroenterologists, scientists, technicians, nurses, expositors and company employees. More than 2000 oral presentations and posters on liver topics were presented. The main themes included: viral hepatitis; cirrhosis; immunology & inflammation; transplantation; tumours; fatty liver disease; drug induced diseases; diagnostics; molecular and cellular biology; paediatric liver diseases; clinical trials; autoimmune diseases; fibrosis markers and public health.

It is not possible to cover in one report all subjects; thus, our summary will focus on new developments in viral hepatitis. Therefore, new discoveries and developments in Hepatitis B, C and D are summarized. The most important clinical trials on new drugs are highlighted in the following, as well as the new products for the treatment of chronic hepatitis B (CHB) in preclinical development and initial clinical trials.

*H*epatitis B: Safety issues surrounding nucleos(t)ide analogue therapies and new developments

The occurrence of malignancies in patients with chronic hepatitis B receiving long term oral nucleos(t)ide analogue (NA) treatment was addressed in a presentation at ILC, raising substantial controversy [1]. The study involved more than 45 000 subjects and indicated that NA treatment does not increase the overall incidence of all malignancies. But significantly higher incidence rates of colorectal cancer and cervical cancer were found in NA-treated CHB patients.

The specialized scientific website Sciencedaily [2] published the comments of Professor Grace Wong, Department of Medicine & Therapeutics Academic, University of Hong Kong and lead study author. "In light of these findings we strongly urge regular screening of these cancers to help prevent them from developing in patients taking nucleos(t)ide analogue treatment." [2]. In addition, Professor Tom Hemming Karlsen, EASL Vice-Secretary declared: "This large-scale study determines an important link between nucleos(t)ide analogue treatment and cervical and colorectal cancer […]. The results are important and could change cancer surveillance and management of patients treated for Hepatitis B." [2].

A Medscape specialized reporter affirmed that after the presentation, the authors revised the statistical management of the data [3], finding non-statistical signification and tuning down the final conclusions to the fact that more data is needed. However, a PLoS ONE 2016 article reported that Entecavir has a clear genotoxic effect inducing DNA damage at nanomolar concentrations in DT40 cells, a DNA repair deficient

1. Wong GLH, Tse YK, Wong V, Yip T, Chan H. Incidences of all malignancies in patients with chronic hepatitis B receiving long-term oral nucleos(t)ide analogue treatment – a study of 45'299 subjects. Section: Viral Hepatitis; Sub-section: Hepatitis B & D -clinical (therapy, new compounds, resistance). Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract PS052.

2. European Association for the Study of the Liver. Treatment for chronic hepatitis B linked to increased rates of colorectal and cervical cancer. ScienceDaily. 2016 Apr 15 [cited 2016 May 30]. Available from: www.sciencedaily.com/releases/2016/04/160415081420.htm

3. Johnson K. Release raises false alarm over Hep B meds and cancer risk. Medscape. 2016 Apr 22 [cited 2016 May 30]. Available from: http://www.medscape.com/viewarticle/862371

4. Jiang L, Wu X, He F, Liu Y, Hu X, Takeda S, *et al*. Genetic Evidence for Genotoxic Effect of Entecavir, an Anti-Hepatitis B Virus Nucleotide Analog. PLoS One. 2016;11(1):e0147440.

5. Food and Drug Administration. Baraclude Product Insert NDA 21-797-S-001. 2007 [cited 2016 May 22]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021797s001,021798s001lbl.pdf

cells [4]. So they propose to monitor the genotoxicity of NAs, especially Entecavir, and to restrict treatment period due to potential risks [4].

Also, the product's inserts of Entecavir and Tenofovir specify carcinogenic effects [5, 6]. Thus, this study need to be followed, taking into account that there is no time limitation to the use of NA in most CHB patients under treatment and that product discontinuation could also be associated to disease exacerbations.

Additionally, results of two works on Phase III clinical evaluations of Tenofovir Alafenamide (TAF), a novel compound for chronic hepatitis B treatment, were presented, one in HBeAg negative patients and the other in HBeAg positive ones. TAF is a prodrug of Tenofovir Disoproxil Fumarate (TFV) that resulted more stable in plasma and delivering TFV into lymphoid cells and hepatocytes while lowering circulating levels of TFV by approximately 90 % as compared to TDF. In patients with HIV, a TAF-containing regime demonstrated a similar efficacy to that of TDF, with significantly reduced bone and renal effects [7].

The study in HBeAg negative patients was designed as placebo controlled, non-inferiority trial and it was conducted in 425 patients, treated at 105 sites from 17 countries, 72 % of them from Asian ethnicity and predominant genotypes C, D and B. Efficacy results evidenced that TAF was non-inferior to TDF in HBeAg negative patients [7]. In addition, patients on TAF experienced significantly less decline in hip and spine bone marrow density (BMD) than TDF, and the glomerular filtration rates and the renal tubular markers also changed less than TAF [8].

In HBeAg positive CHB patients, the Phase III study of TAF compared with TDF [9] was also designed as placebo controlled, non-inferiority trial and it was conducted in 873 patients, treated at 164 sites from 19 countries, 82 % of them from Asian ethnicity and predominant genotypes C, D and B, in this order. A similar efficacy in term of antiviral effect and superiority in ALT normalization was also found in the subset of HBeAg positive patients. HBeAg-positive patients on TAF experienced significantly less declines in hip and spine BMD than TDF and a significantly lower increase in serum creatinine. The glomerular filtration rates and the renal tubular markers also changed less than TAF. It is important to highlight the disappointing levels of HBeAg seroconversion found in the 873 patients of this trial, only 10 % in TAF and 8 % in TDF [9].

The NA therapy is currently not recommended to immune tolerant patients. A presentation from the Seoul National University Hospital explored the impact of the antiviral treatment for immune tolerant phase CHB patients. The study was planned as a single center, retrospective study involving 644 patients in this phase of the disease. A total of 54 patients were included in the treatment group. By log-rank test there was no difference between groups in terms of appearance of hepatocellular carcinoma (HCC), liver cirrhosis (LC) or overall survival (OS). However, a multivariate Cox analysis, showed significantly lower risk of HCC and LC in the treatment group. The treatment group showed longer overall survival when baseline characteristics in both groups were balanced [10]. In our opinion, the reduced number of treated patients and the statistical contradictions will not create a strong recommendation for treating these patients; however, all companies producing CHB therapies are developing clinical trials to cover this scenario in the future, according to the indexed clinical trials at NIH database.

Novira Therapeutics, a company developing the first-in-class HBV core inhibitor NVR 3-778, reported its use alone and in combination with Peg-Interferon (PegIFN), in treatment-naïve HBeAg-positive patients [11]. This Phase 1b trial enrolled 64 patients in NVR 3-778 treatment cohorts or placebo: 6 groups with dose escalating levels of the product and 2 additional groups receiving placebo. The study lasted 28 days. The doses tested were 100, 200 and 400 mg daily and 600 mg twice daily in the first 4 groups, the other two groups received combined 600 mg/PegIFN and placebo/PegIFN. The assayed product was well tolerated, with no appreciable dose-related adverse events. Dose-related HBV DNA and early HBeAg reductions were observed and increased in the PegIFN combined group. A phase II study was designed to evaluate whether longer duration of NVR 3-778 with and without Peg-IFN achieves sustained and improved rate of HBeAg seroconversion that are durable post-treatment [11].

The consolidation of the direct acting antivirals revolution

The infection with the genotype 3 (GT3) of the HCV accounts for the 30 % of all HCV infections at the global scale [12]. The GT3 is also associated with a higher risk of liver steatosis, hepatocellular carcinoma and fibrosis progression than other genotypes. It is more difficult to cure than other genotypes, especially in patients with cirrhosis. Currently approved guidelines for patients with GT3 HCV infection and cirrhosis results in sustained virological response at week 12 post treatment (SVR12) rates of 79 to 88 %. The next-generation direct-acting antivirals (DDAs) in development: ABT-493, a pangenotypic NS3/4A protease inhibitor and the ABT-530, a pangenotypic NS5A inhibitor, have several advantages: are synergistic therapeutics with elevated barrier to resistance, antiviral activity against typical NS3 and NS5A resistance associated variants (RAVs), minimal metabolism and primarily biliary excretion and feasible once-daily oral dosing.

After a 100 % SVR12 after 8 or 12 weeks of ABT-493 plus ABT-530 in treatment naive patients with GT3 HCV infection without cirrhosis, the intent-to-treat analysis was modified to evaluate the efficacy, safety of ABT-493 plus ABT-530 with or without ribavirin in treatment-naive patients with GT3 HCV infection and compensated cirrhosis as a phase II trial in 48 patients. The results of the SURVEYOR-II (after intent-to-treat modification to include in the study compensated cirrhosis patients)[13] are described in the table. Treatment-naive patients with genotype 3 hepatitis C virus (HCV) infection and compensated cirrhosis, 12 weeks of once-daily ABT-493 and ABT-530 with or without ribavirin resulted in 100 % SVR12. The regimen was generally well tolerated, with no discontinuations due to adverse events [13].

6. Food and Drug Administration. Viread Product Insert. 2012 [cited 2016 May 22]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021356s042,022577s002lbl.pdf

7. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.

8. Buti M, Gane E, Seto WK, Chan HLY, Chuang WL, Stepanova T, *et al*. A phase III study of Tenofovir Alafenamide compared with Tenofovir Disoproxil Fumarate in patients with HBeAg-negative, chronic hepatitis B: Week 48 efficacy and safety results. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract GS06.

9. Chan HLY, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, *et al*. A phase III study of Tenofovir Alafenamide compared with Tenofovir Disoproxil Fumarate in patients with HBeAg-positive, chronic hepatitis B: Week 48 efficacy and safety results. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract GS12.

10. Chang Y, Lee JH, Nam JY, Ahn H, Cho H, Cho Y, *et al*. Nucleos(t)ide analogue treatment for immune tolerant phase of Chronic Hepatitis B patients prolongs overall survival and reduces the risk of hepatocellular carcinoma and cirrhosis: a real-life study. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract PS049.

11. Yuen MF, Kim DJ, Weilert F, Chan HLY, Lalezari JP, Hwang SG, *et al*. NVR 3-778, A first in class HBV core inhibitor, alone and in combination with Peg-Interferon (PegIFN), in treatment-naïve HBeAg-positive patients: Early reductions in HBV DNA and HBeAg. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract, Late Breaker.

12. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, *et al*. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77-87.

13. Kwo PY, Wyles DL, Wang S, Poordad F, Gane E, Maliakkal B, *et al*. SURVEYOR-II: 100% SVR12 with ABT-493 and ABT-530 with or without ribavirin in treatment-naive HCV genotype 3-infected patients with cirrhosis. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract LBO1.

Table. Main therapeutic trials against hepatitis C virus and their major findings, presented at the at the 2016 Annual Meeting of the European Association for the Study of the Liver (EASL), International Liver Congress (ILC), held in Barcelona, Spain, from April 13th to 17th

Title of the trial [reference]	Study design in brief	Conclusions
SURVEYOR-II: a partially randomized, open-label, multicenter phase II trial [14]	- Phase II study to evaluate 2 treatment schedules using ABTs DAA. Treatment-naive patients with GT3 HCV and compensated cirrhosis received 12 weeks of once-daily ABT-493 and ABT-530 with or without RBV. Two groups of 24 patients *Main inclusion criteria*: 18-70 years of age; GT3 HCV infection; HCV RNA > 10,000 IU/mL; Compensated cirrhosis (Child-Pugh score ≤ 6); Liver biopsy (METAVIR > 3 or Ishak > 4), or FibroScan ≥ 14.6 kPa, or FibroTest ≥ 0.75 with aspartate aminotransferase (AST)–to-platelet ratio index > 2 *Main Exclusion criteria*: Previous HCV treatment; History of hepatic decompensation; HIV coinfection; Albumin below lower limit of normal; Platelet count < 90 × 10^9 /L	100% SVR12 post treatment Presence of baseline NS3 and/or NS5A RAVs had no impact on regimen efficacy in this population. Regimen generally well tolerated; no discontinuations due to AEs The combination is being evaluated across genotypes as RBV-free therapy in 8-week and 12-week regimens for patients with and without cirrhosis and 12-week regimen for patients with compensated cirrhosis
HCV-TARGET: interim analysis of a multicenter, prospective, observational cohort study [15]	Exploratory study to assess the prevalence of RAVs in patients with genotype 1 HCV infection in real-world setting and the impact of RAVs on patient response to LDV/SOF with or without RBV or SMV plus SOF with or without RBV. Participants from HCV-TARGET who consented to phlebotomy prior to beginning HCV treatment RAVs assessed using Monogram Biosciences sequencing assay (10 % variant reporting threshold) N = 494 patient samples analyzed, of which 2 gave indeterminate results N = 492 evaluable patients included in assessment of RAV prevalence 98 % had available data for NS3 (n = 486), NS5A (n = 490), NS5B (n = 486) GT1a HCV in 75.6 %, GT1b in 24.4 % N = 472 patients included in DAA efficacy analysis	Analysis of RAVs in patients infected with GT1 hepatitis C virus (HCV) who received LDV/ SOF or SMV plus SOF, each with or without RBV, in real-world settings detected NS3 RAVs in 45%, NS5A RAVs in 13 %, and NS5B RAVs in 8 % of patients NS3 RAVs more common in patients with GT1a HCV and the most common NS3 RAV: Q80K/R NS5A and NS5B RAVs more common in patients with GT1b HCV and the most common NS5A RAV: Y93C/H/N; most common NS5B RAV: S556G Prevalence of RAVs comparable across cirrhotic vs. non-cirrhotic, treatment-naive vs. treatment-experienced, and transplanted vs. not transplanted patient populations SVR rates across patient subgroups did not differ significantly according to presence of baseline RAVs overall Y93C/H/N detected infrequently in patients receiving LDV/ SOF (4 %) but associated with significantly reduced SVR12 rate (96 % without vs 75 % with RAVs; P = 0.046)
German HEPNET Acute HCV (IV): a single-arm, prospective, multicenter pilot study [16]	A pilot study aimed at evaluating the efficacy of LDV/SOF administered for 6 weeks in patients with acute GT1 HCV monoinfection. Acute HCV infection defined as: Known or suspected HCV exposure in past 4 months; documented seroconversion to anti-HCV antibodies; ALT level > 10 × ULN *Inclusion criteria*: 18 years of age or older; HCV RNA > 1000 IU/mL; Compensated liver disease IV negative. Hepatitis B surface antigen negative. *Treatment*: SOF fixed-dose combination administered daily for 6 weeks	In patients with acute genotype 1 hepatitis C virus (HCV) monoinfection, a 6-week interferon (IFN)-free regimen of ledipasvir (LDV)/sofosbuvir (SOF) was associated with sustained virologic response rate at 12 weeks post treatment (SVR12) of 100 % The virologic response slower in patients with higher baseline HCV RNA levels. The ALT and bilirubin levels returned to normal rapidly in majority of patients. The treatment for 6 weeks of LDV/SOF was well tolerated in the acute infection setting Evaluation of shorter course LDV/SOF therapy in acute setting warranted
HEPA-C Registry: retrospective, observational cohort study [17]	A retrospective, observational cohort study assessed outcomes of DAA therapy in cirrhotic patients (CTP A vs B/C) enrolled in the HEPA-C Spanish national registry for HCV-infected patients: selected those receiving DAA therapy w/o IFN from April 2013 to December 2015: N = 843 *Eligibility*: Cirrhosis on biopsy, FibroScan, and/or clinical symptoms; No liver transplantation during HCV treatment or within 12 weeks of end of treatment *Study aims*: Assess efficacy, safety of treatment in overall population and according to CTP score; Identify predictors of severe AEs & death *Patient disposition*: n = 170 on treatment, Week 0-12. N = 673 with Week 12 follow-up data available	Among cirrhotic, HCV–infected patients receiving DAA therapy in a real-world cohort, patients with CTP class A disease experienced higher SVR rates, fewer severe AEs, and less risk of death vs. patients with decompensated cirrhosis (CTP B/C) SVR: 94 % with CTP A vs 78% with CTP B/C (P < 0.001) Serious AE: 12 % vs 50 %, respectively (P < 0.001) Death: 0.9 % vs 6.4 %, respectively (P < 0.001) MELD ≥ 18 independently predicted severe AEs and death (P < 0.001)
ASCEND Investigation: a multi-center, open label, phase IV, non-randomized clinical trial [18]	Longitudinal trial to evaluate the efficacy and safety of complete task shifting of HCV therapy using DAA to community-based non-specialist providers. Chronic HCV infected patients of community health centers received non-randomized treatment from either a specialist (Hepatologists), primary care physician (PCP), or nurse practitioner (NP). Providers underwent three hours training on AASLD HCV guidelines and patients were treated with LDV/SOF as per FDA label The primary outcome was defined as unquantifiable HCV RNA 12 weeks after the end of treatment (SVR12) A total of 600 patients began treatment with LDV/SOF from May to Nov 2015, with follow-up ongoing Patients were predominantly black (96 %) and GT1a (72 %). From them, 24 % were HIV/HCV coinfected, 18 % were treatment experienced and 20 % cirrhotic by biopsy. Baseline characteristics were similar among treatment groups	The first interim analysis of the Ascend Investigation was conducted after more than 50% of the patients (304 patients) arrived to week 12 follow-up, a total of 285 achieved SVR12 (93.8% per protocol; 88.2% intention to treat) Only GT1a was associated with virologic failure (p=0.003). There was no significant difference (p=0.48) in SVR12 between provider types: NPs (75/79; 94.9 %), PCRs (58/60; 96.7 %), and specialists (152/165; 92.1 %) From the 409 patients completing 12 weeks of therapy, significantly lower composite visit adherence was observed in specialist-led treatment (p<0.001) HCV treatment administered independently by non-specialist providers is safe and equally effective to that observed with experienced specialists, inclusive with challenging subpopulations. These results could increase the availability of community-based, non-specialist providers to significantly expand the scale of HCV therapy and bridge existing gaps in the hepatitis C care cascade

AE: Adverse events; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CTP: Child-Turcotte-Pugh; DAA: Direct-acting antiviral; GT: Genotype; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; LDV: Ledipasvir; MELD: Model for End-Stage Liver Disease; RAVs: resistance associated variants; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; SVR: Sustained virological response; ULN: Upper limit of normal; w/o: without.

Regarding the data describing prevalence of baseline resistance associated variants (RAVs) in diverse HCV-infected populations, it is limited and the effect of RAVs on response to HCV treatment in real-world settings has not been well established. The objective of the HCV-TARGET study [14] was to explore the prevalence of RAVs in patients with genotype 1 HCV infection in real-world setting and assess impact of RAVs on patient response to Ledipasvir (LDV)/Sofosbuvir (SOF) with or without ribavirin (RBV) or simeprevir (SMV) plus SOF with or without RBV. The analysis of RAVs detected NS3 RAVs in 45 %, NS5A RAVs in 13 %, and NS5B RAVs in 8 % of patients. The NS3 RAVs were found more common in patients with genotype 1a HCV and the most common NS3 RAV: Q80K/R. The most common NS5A and NS5B RAVs (Y93C/H/N and S556G, respectively) were the most common in patients with genotype 1b HCV. The prevalence of RAVs was comparable across cirrhotic vs. non-cirrhotic, treatment-naive vs. treatment-experienced, and transplanted vs. not transplanted patient populations [14].

The young adults who inject drugs are at high risk of HCV infection. Half of acutely infected HCV patients clear infection spontaneously. The early intervention with interferon (IFN)-based treatment during the acute infection is highly effective for preventing the chronic infection. The german acute HCV studies I-III demonstrated efficacy of various IFN-based regimens in patients with acute HCV infection [15]. The efficacy and safety of IFN-free DAA-based regimens have not been well studied in patients with acute HCV monoinfection. A single-arm, prospective, multicenter pilot study (HepNet Acute HCV (IV) study) was aimed at evaluating the efficacy of LDV/SOF administered for 6 weeks in patients with acute genotype 1 HCV monoinfection [15].

In patients with acute genotype 1 HCV monoinfection, a 6-week IFN-free regimen of LDV/SOF was associated with SVR12 of 100 %. The virologic response was slower in patients with higher baseline HCV RNA levels. The ALT and bilirubin levels returned to normal rapidly in majority of patients. The treatment for 6 weeks of LDV/SOF was well tolerated in the acute infection setting. The authors consider that the findings must be confirmed in other HCV genotypes and with other regimens, but IFN-free DAA regimen may be considered for treating patients with HCV acute hepatitis. These results open the window to future assessments of a shorter course of LDV/SOF therapy in acute setting [15].

Another key trial presented was the HEPA C Registry, a retrospective, observational cohort study, which assessed the outcomes of DAA therapy in cirrhotic patients (Child-Turcotte-Pugh score (CTP) A vs. B/C) enrolled in the HEPA-C Spanish national registry for HCV-infected patients. It assessed the efficacy, safety of treatment in the overall population and according to CTP score, and identified predictors of severe adverse events and death. Patients receiving DAA therapy without PegIFN treatment from April 2013 to December 2015 (n = 843) were selected for the study, if they present cirrhosis on biopsy, FibroScan evaluation and/or clinical symptoms. Liver transplantation during HCV treatment or 12 weeks follow-up were exclusion criteria [16]. The patients with CTP class A disease experienced higher SVR rates, fewer severe adverse events, and less risk of death, compared to the patients with decompensated cirrhosis (CTP B/C). The sustained virological response was 94 % with CTP A and 78 % with CTP B/C, for a highly significant difference ($p < 0.001$). The serious adverse events were also different: 12 vs. 50 %, respectively ($p < 0.001$), and the appearance of death also rose significantly with the CTP level: 0.9 vs. 6.4 %, respectively ($p < 0.001$) [16].

One of the studies presented at the ILC that better represent the consolidation of the DAA revolution in the treatment of the chronic hepatitis C is the Ascend Investigation [17]. This is a longitudinal trial to evaluate the efficacy and safety of complete task shifting of HCV therapy using DAA to community-based non-specialist providers. Planned as a multi-center, open label, phase IV clinical trial, chronic HCV infected patients of community health centers received non-randomized treatment from either a specialist (Hepatologist), primary care physician (PCP), or nurse practitioner (NP). Providers underwent three hours training on the American Association for the Study of Liver Diseases (AASLD) HCV guidelines and patients were treated with LDV/SOF as per the Food and Drugs Administration (FDA) label. The primary outcome was defined as unquantifiable HCV RNA 12 weeks after the end of treatment (SVR12). A total of 600 patients began treatment with LDV/SOF from May to Nov 2015, with follow-up ongoing. Patients were predominantly black (96 %) and GT1a (72 %). From them, 24 % were HIV/HCV coinfected, 18 % were treatment experienced and 20 % cirrhotic by biopsy. Baseline characteristics were similar among treatment groups.

The first interim analysis of the Ascend Investigation was conducted after more than 50 % of the patients (304 patients) arrived to week 12 follow-up, a total of 285 achieved SVR12 (93.8 % per protocol; 88.2 % intention to treat). Only GT1a was associated with virologic failure ($p = 0.003$). There was no significant difference in SVR12 between provider types: NPs, PCRs, and specialists. From the 409 patients completing 12 weeks of therapy, significantly lower composite visit adherence was observed in specialist-led treatment ($p < 0.001$). In conclusion, this study demonstrated that the HCV treatment administered independently by non-specialist providers is safe and equally effective to that observed with experienced specialists, inclusive in difficult-to-treat subpopulations. These results could increase the availability of non-specialist providers based at the community to expand HCV treatments, bridging existing gaps in the hepatitis C care cascade [17].

Does antiviral treatment affect outcome of Hepatitis Delta?

Hepatitis Delta, the most severe form of viral hepatitis, and its therapy are still a matter of research. A very enlightening retrospective study developed by the Medical School of Hannover was aimed at exploring the long term benefit of interferon based treatments, NA treatment or non-treating the delta patients.

14. Wang GP, Reeves JD, Terrault N, Lim JK, Morelli G, Kuo A, *et al*. Prevalence and impact of baseline resistance-associated variants on the efficacy of ledipasvir/sofosbuvir or simeprevir/sofosbuvir against GT1 HCV infection: HCV-TARGET interim analysis. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract PS102.

15. Deterding K, Spinner C, Schott E, Welzel T, Gerken G, Klinker H, e. Six weeks of sofosbuvir/ledipasvir (SOF/LDV) are sufficient to treat acute hepatitis C virus genotype 1 monoinfection: the HEPNET Acute HCV IV Study. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract LBO8.

16. Fernández-Carrillo C, Lens S, Llop E, Pascasio JM, Fernandez I, Baliellas C, *et al*. Treatment of hepatitis C virus in patients with advanced cirrhosis: always justified? Analysis of the HEPA-C registry. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract GS01.

17. Kattakushy S, Gross C, Teferi G, Jenkins V, Silk R, Akoth E, *et al*. A novel task shifting model to expand the HCV care continuum: the ascend investigation. Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract LBP524.

From more than 350 anti HDV-positive patients treated at the Hannover Medical Hospital between 1987 and 2012, 136 individuals followed for at least 6 months were selected for the study. The median time follow-up was 5.2 years, mean age 38 years and 67 % were male. Cirrhosis was found in 62 patients as first presentation. Clinical endpoints defined as hepatic decompensation (ascites, encephalopathy, variceal bleeding), hepatocellular carcinoma, orthotopic liver transplantation or death occurred in 55 patients (40 %). During follow-up, 29 % of patients did not receive any antiviral treatment, 38 % were treated with IFN α-based therapies and 33 % received HBV polymerase inhibitors (recycling nucleos(t)ides; NUCs) only [16].

The results of this study demonstrated that patients who received IFNα-based therapies developed less frequently clinical endpoints than patients treated with NUCs ($p < 0.01$) or untreated patients ($p < 0.01$) in χ-square analysis. IFNα-based therapies was also associated with a more benign outcome compared to untreated ($p = 0.05$) and NUC-treated patients ($p = 0.02$) in time-dependent Kaplan Meier analysis. Previous IFNα therapy ($p = 0.03$) and presence of cirrhosis ($p = 0.05$) were independently associated with the clinical long-term outcome in multivariate analysis [18].

Hepatitis delta infections can only occur in those who are infected with Hepatitis B. According to the EASL guidelines, pegylated interferon is the only treatment effective against Hepatitis delta. As declared by Anika Wranke, leading reasercher of the study and Fellow of Hannover Medical School, Germany, at the venue [19]: "There has been significant debate over whether there are long-term benefits to patients with Hepatitis delta receiving antiviral treatment… Our study demonstrates that the long-term outcomes for patients with severe Hepatitis delta, who have limited treatment options, could be improved with a widely available medication.".

In our opinion, this study is a fundamental knowledge for countries were delta virus may be in high prevalence because it is demonstrating that the use of antivirals does not modify the appearance of the specified clinical endpoints compared to no treatment, in contrast to PegIFN therapy. In countries with a relevant percentage of CHB could be infected with the delta virus, the serological evaluation of delta may be useful to correctly define the treatment option. The reason, in few words: the study demonstrated that 35 % of patients with Hepatitis delta who responded to IFNα based therapies achieved sustained suppression of the virus and had favourable outcomes compared to those untreated or treated with nucleos(t)ide analogues. This work is a remarkable contribution in the definition of treatment options against delta virus.

ILC: A conference surrounded by demonstrators

The present edition of the ILC was surrounded by important demonstrations from patients, families and activists from the civil society coming from different cities of Spain. Government and companies were demanded for reductions in the cost of drugs, special prominence received the abusive cost of the novel DAAs used for chronic hepatitis C (CHC) treatment, and the narrow policies for patients' treatment coverage reaching only advanced cases of liver damage. Demonstrators referred to the press and scientists at the convention center that their relatives died waiting for treatment approval or because of the late start of their therapies.

Acknowledgements

Many thanks to Professor Christian Trepo, from the Service of Hepatogastroenterology, CHU de Lyon HCL - GH Nord-Hôpital de la Croix Rousse,Lyon, France, for his kindful review and insightful comments on the manuscript.

18. Wrankle A, Serrano BC, Heidrich B, Kirschner J, Bremer B, Hardtke S, *et al*. Does antiviral treatment affect the clinical long-term outcome of Hepatitis Delta? Section: Viral Hepatitis; Sub-section: Hepatitis B & D –clinical (therapy, new compounds, resistance). Program and abstracts of the 51st Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain. Abstract GS053.

19. European Association for the Study of the Liver. Study demonstrates benefits of existing treatment for hepatitis D patients. ScienceDaily. 2016 Apr 15 [cited 2016 May 30]. Available from: https://www.sciencedaily.com/releases/2016/04/160415081411.htm