# *Highlights from Barcelona 2012 International Liver Congress and EASL meeting*

REPORT

Julio C Aguilar

Departamento de Vacunas, Dirección de Investigaciones Biomédicas,
Centro de Ingeniería Genética y Biotecnología, CIGB
Ave. 31 e/ 158 y 190, Cubanacán, Playa, CP 11600, La Habana, Cuba
E-mail: julio.aguilar@cigb.edu.cu

***ABSTRACT***

The International Liver Congress 2012 took place at the Centre de Convencions Internacional de Barcelona (CCIB), Spain, on April 18-22. This venue was the 47th annual meeting of the European Association for the Study of the Liver (EASL). The most important novelties of these two events are summarized in the present report.

*Keywords*: International Liver Congress 2012, EASL, hepatitis C virus, hepatitis therapy, diabetes, gut microbiota

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***RESUMEN***

**Destaques del Congreso Internacional del Hígado y reunión de la EASL, Barcelona 2012.** El Congreso Internacional del Hígado del año 2012 se celebró en el Centro de Convenciones Internacional de Barcelona (CCIB), España, del 18 al 22 de abril. En esta ocasión coincidió con la 47 Convención Anual de la Asociación Europea para el Estudio del Hígado (EASL). Se describen en este reporte las novedades más relevantes de estos dos importantes eventos.

*Palabras clave*: Congreso Internacional del Hígado 2012, EASL, virus de la hepatitis C, terapia de la hepatitis, diabetes, flora microbiana

## *I*ntroduction

The International Liver Congress 2012 organized by the European Association for the Study of the Liver (EASL) was held in Barcelona, Spain, at the Centre de Convencions Internacional de Barcelona (CCIB), on April 18-22, 2012.

The meeting evidenced the consolidation of the interferon-free revolution in hepatitis C virus (HCV) treatment as most outstanding topic. The studies related to the true impact that liver disease has across Europe in terms of mortality and costs were also highlighted. At preclinical level, studies in mice significantly evidenced that gut microbiota transplantation may prevent the development of diabetes and fatty liver disease.

## *N*ew data suggests interferon-free therapy around the corner for hepatitis C patients

The much anticipated data from a number of clinical trials [1-6] confirmed that combinations of antivirals offer the hope of shorter, more effective treatment with fewer side effects compared to the 2012 standard of care using interferon.

The new studies cover the treatment of patients infected with hepatitis C virus (HCV) genotypes (GT) 1 to 3, who were administered ribavirin (RBV) without interferon (IFN) and either one or two other drugs: direct-acting antivirals, such as HCV nucleotide analogues, HCV protease inhibitors, non-nucleoside RNA polymerase inhibitors, or host-targeting antivirals like the inhibitor cyclophilin A.

The combination of pegylated interferon alpha (PegIFN-α) and RBV is the current standard of care for chronic HCV [7], but it is associated with a number of side effects - including flu-like symptoms, psychiatric manifestations, autoimmune reactions, and hematologic toxicities [8, 9]. Between 20-40 % of patients require a dose reduction or temporary interruption in their PegIFN-α and RBV treatment [10], and in 10-14 % the side effects are so severe that treatment must be interrupted [8, 9].

Studies have shown that PegIFN-α free therapy is highly anticipated by healthcare professionals and patients alike. The EASL's Secretary General, Professor Mark Thursz commented on the exciting new data being showcased at the congress: "In the future, patients can look forward to all oral treatment regimens with high success rates and low side effects. Furthermore, there is a large cohort of patients with more advanced liver disease who will now be able to access treatment that was previously impossible due to the side effects of Interferon-alpha. Over the last five years we have seen an evolution in HCV treatment, with direct antivirals used in combination with Pegylated Interferon and Ribavirin. Interferon-free regimes truly represent a revolution in treatment."

Separate data presented at the congress may provide a further option. New results from a phase IIb study show a different form of interferon: PegIFN-λ, administered with RBV for 24 weeks in HCV GT2 & 3 patients give comparable undetectable HCV RNA levels 24 weeks after treatment as those treated with PegIFN-α-2a and RBV, but with fewer side effects (musculoskeletal and flu-like symptoms, hematologic toxicity) and dose modifications for PegIFN or RBV. Professor Thursz commented: "It remains possible that a number of patients will still need interferon based therapy for their HCV infection. Interferon-lambda, with a better side effect profile, looks like an excellent option in this group of patients, who are likely to have more advanced disease."

Some of the above studies, together with the most relevant works on this topic presented in the meeting are summarized in the table [1-3, 6, 11-16].

1. Lawitz E, Gane E, Stedman C, Lalezari JP, Hassanein T, Kowdley KV, *et al*. 7 PSI-7977 PROTON and ELECTRON: 100 % concordance of SVR4 with SVR24 in HCV GT1, GT2 & GT3. J Hepatol. 2012;56 (Suppl 2):S4.

2. Gane EJ, Stedman CA, Hyland RH, Sorensen RD, Symonds WT, Hindes RG, *et al*. ELECTRON: once daily PSI-7977 plus RBV in HCV GT1/2/3. J Hepatol. 2012;56 (Suppl 2):S438-9.

3. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse A, Muellhaupt B, *et al*. SVR4 and SVR12 with an interferon-free regimen of BI201335 and BI207127, +/- Ribavirin, in treatment-naive patients with chronic genotype-1 HCV infection: Interim results of SOUND-C2. J Hepatol. 2012;56(Suppl 2):S45.

4. Pawlotsky JM, Sarin SK, Foster G, Peng CY, Rasenack J, Flisiak R, *et al*. Alisporivir plus Ribavirin is highly effective as interferon-free or interferon-add-on regimen in previously untreated HCV-GT2 OR GT3 patients: SVR12 RESULTS FROM VITAL-1 PHASE 2B STUDY. J Hepatol. 2012; 56(Suppl 2):S553.

5. Alberti A, Chuang WL, Flisiak R, Mazzella G, Horban A, Goeser T, *et al*. ALISPORIVIR (ALV) plus PEG-Interferon/ Ribavirin (PR) IN HCV G1 treatment-experienced patients achieves primary endpoint with superior efficacy at treatment week 12 compared to retreatment with PR. J Hepatol. 2012;56(Suppl 2):S553-4.

6. Sulkowski M, Gardiner D, Lawitz E, Hinestrosa F, Nelson D, Thuluvath P, *et al*. Potent viral suppression with all-oral combination of DACLATASVIR (NS5A inhibitor) and GS-7977 (NS5B inhibitor), +/- Ribavirin, in treatment-naive patients with chronic HCV GT1, 2, OR 3. J Hepatol. 2012;56(Suppl 2):S560.

7. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2011;55(2):245-64.

Table. Summary of the most important results in the field of novel therapies against chronic hepatitis C, presented at the Barcelona 2012 International Liver Congress and EASL meeting

| Study (type) | Key results | Ref. |
|---|---|---|
| IFN-free combination of Daclatasvir (NS5A inhibitor) plus GS-7977 (NS5B inhibitor), once daily, oral route (randomized, open-label, parallel-group phase IIa trial) | High rate of SVR4 in non-cirrhotic treatment-naive patients with GT1, 2 or 3 HCV infection<br>100 % SVR4 in GT1 HCV infected patients, with or without RBV, regardless *IL28B* genotype or HCV subtype<br>More than 90 % SVR4 rate in patients with GT2 or 3 HCV infection without RBV<br>Daclatasvir plus GS-7977 was safe and tolerable<br>No grade 3 or 4 ALT, AST, or total/direct bilirubin elevations | [6] |
| IFN-free regimen of ABT-450 / Ritonavir, ABT-072, ABT-450, and RBV (pilot study: single-arm open-label pilot study) | Robust treatment response in 12 weeks of combination therapy with ABT-450/ritonavir + ABT-072 + RBV in treatment-naive, non-cirrhotic, GT1 HCV-infected patients with *IL28B*-CC genotype induced an extended rapid virologic response in all the patients<br>SVR12 in 91 % of patients and SVR36 in 82 %<br>Therapy well tolerated over 12 weeks of treatment, no virologic breakthroughs on therapy and only two relapses post-therapy | [12] |
| Dual oral therapy with Daclatasvir and Asunaprevir in GT1b HCV-Infected patients with previous null response, medical ineligibility, or intolerance to PegIFN / RBV (subanalysis of open-label phase IIa study) | IFN-free regimen of Daclatasvir plus Asunaprevir produced 77 % overall SVR24 in difficult-to-treat patients with GT1b HCV infection<br>Virologic breakthrough and relapse infrequent, associated with preexisting NS5A Y93H polymorphism<br>Tolerable toxicity profile | [12] |
| SOUND-C2 Interim Results: High Efficacy, Good Safety Profile of IFN-Free BI 201335, BI 207127, and RBV Combination Therapy in GT1 HCV Treatment-Naive Patients (interim analysis of SOUND-C2: randomized, open-label phase IIb study) | Sustained SVR4 to SVR12 rates in 56 to 68 % of patients<br>Highest SVR (up to 82 %) either in GT1b or GT1a HCV patients, regardless having genotype *IL28B*-CC or not<br>RBV necessary to attain high SVR rates<br>Favorable safety and tolerability profile of BI 201335 plus BI 207127 plus RBV<br>Twice-daily vs. thrice-daily BI 207127 dosing provided best tolerability with low rate of treatment discontinuation<br>Most common adverse events and laboratory abnormalities: gastrointestinal events, skin reactions, and hyperbilirubinemia; very little impact on hematologic parameters | [3] |
| ELECTRON. Interferon is not required for SVR in treatment-naive GT2 or GT3 HCV patients | 100 % SVR in ELECTRON in HCV GT2/3 on interferon-free PSI-7977/RBV | [14] |
| ELECTRON: Once daily PSI-7977 plus RBV in HCV GT1/2/3 (additional cohorts enrolled to ELECTRON study to explore shorter duration of therapy and difficult to treat populations treated with PSI7977 and RBV) | PSI-7977 demonstrated above 90 % SVR in PROTON in HCV GT1, GT2/3 with pegIFN-$\alpha$/RBV, and 100 % SVR in ELECTRON in HCV GT2/3 on interferon-free PSI-7977/RBV<br>IFN-free, oral PSI-7977/RBV showed consistent antiviral suppression across HCV genotypes, independent of traditional predictors of poor responsiveness to IFN or prior non-response to pegIFN-$\alpha$/RBV<br>High on-treatment response and lack of viral resistance, even in the absence of pegIFN-$\alpha$; confirms the high barrier to resistance in this GT1 patients population<br>Preliminary safety review revealed no discontinuations and no SAEs | [2] |
| Combined PSI-7977 400 mg QD safety and tolerability in the first 450 patients treated for 12 weeks (Metanalysis PROTON, ELECTRON and ATOMIC studies, including PSI-7977/RBV and PSI/pegIFN-$\alpha$/RBV) | Analysis of combined safety across PSI-7977 Phase 2 studies<br>All available safety data aggregated by regimen: (a) PSI-7977, (b) PSI-7977/RBV, (c) PSI-7977/pegIFN-$\alpha$/RBV<br>AEs and SAEs, discontinuations, and safety laboratory values included<br>Once-daily PSI-7977 400 mg as monotherapy, with RBV, or with pegIFN-$\alpha$/RBV generally safe and well-tolerated over the intended 12 week dosing period<br>No PSI-7977-attributable SAEs, and no increase in study discontinuations in cohorts receiving PSI-7977 with pegIFN-$\alpha$/RBV<br>Interferon-free PSI-7977/RBV and PSI-7977 monotherapy gighly tolerated for 12 weeks, with no discontinuations and a clinically-significant improvement in adverse events and hematologic abnormalities<br>No specific laboratory or other safety signal observed across the PSI-7977 development program | [13] |
| PSI-7977 PROTON and ELECTRON: 100 % concordance of SVR4 with SVR24 in HCV GT1-3 (Metanalysis) | PSI-7977 end-of-therapy response > 90 % and SVR12 in IFN-containing and IFN-free regimes, in HCV GT1-3<br>Positive and negative predictive values of SVR4 and SVR12 for viral cure (SVR24) assessed<br>One hundred and seventeen subjects with HCV GT1-3 received PSI-7977 400 mg QD in ELECTRON or PROTON and achieved HCV RNA below the limit of detection at end-of-therapy<br>Four out of ten subjects on PSI-7977 monotherapy experienced relapse, versus 1 in 107 receiving PSI-7977/RBV with or without pegIFN-$\alpha$<br>Relapses within 4 weeks after therapy discontinuation, with no relapse across the PSI-7977 program after SVR4, regardless treatment duration<br>Absence of on-treatment viral breakthrough and lack of relapse after SVR4 indicate suppression beyond the dynamic range of current assays, and confirm the high barrier to resistance of PSI-7977<br>Data from the PSI-7977 development program support the potential use of SVR4 as biomarker of viral cure in HCV | [1] |
| ATOMIC: 97 % rapid virologic response for PSI-7977 + pegIFN-$\alpha$/RBV $\alpha$ 12 weeks regimen in GT1 HCV patients | No on-treatment virologic breakthrough<br>More than 92 % SVR4; 90 % SVR12 in the 12-week treatment arm<br>Virologic relapse rare, with no S282T mutations detected<br>Efficacy of 12 weeks' combination therapy comparable to that of 24 weeks' combination therapy<br>GS-7977 safe and well tolerated in combination with pegIFN/RBV for up to 24 weeks | [15] |
| Co-pilot study: IFN-free regimen of ABT-450/Ritonavir, ABT-333, and RBV achieved SVR12 > in 93-95 % of GT1 HCV patients (Interim analysis of co-Pilot exploratory study: non-randomized, prospective, open-label phase II trial) | No patient who completed treatment experienced virologic failure<br>Lower SVR (47 %) in patients with previous nonresponse to pegIFN/RBV<br>ABT-450/ritonavir, ABT-333, and RBV safe and well tolerated<br>Adverse events generally mild<br>Transient asymptomatic increases in bilirubin attributed to ABT-450 | [16] |

AEs: adverse events; GT: genotype; IFN: interferon; pegIFN: pegylated interferon; RBV: ribavirin; SVR: sustained virologic response at the indicated week number post-treatment; Ref.: reference; RVR: rapid virologic response; SAEs: serious adverse events.

Definitively, the development of interferon free therapies will impact in the currently established guidelines for chronic hepatitis C therapy in the next two or three years.

## Gut microbiota transplantation prevents development of diabetes and fatty liver disease in preclinical studies

The factors leading to non-alcoholic fatty liver disease (NAFLD) are poorly understood, but it is known that NAFLD and type 2 diabetes are characterized by liver inflammation and metabolic disorders like insulin resistance, respectively. New data presented at the meeting showed the gut microbiota as having a causal role in the development of diabetes and NAFLD, independent of obesity [17].

Though at an early stage of animal model development, a French study highlights the possibility of preventing diabetes and NAFLD with gut microbiota transplantation, the engrafting of new microbiota, usually through administering faecal material from a healthy donor into the colon of a diseased recipient [18].

In the 16 weeks of the study, two groups of germ free mice received gut microbiota transplants; one set from donor mice displaying symptoms of insulin resistance and liver steatosis (responders), and the other from normal mice (non responders). The donor mice were selected due to their response to feeding with a high fat diet. The germ free group that received microbiota from symptomatic mice showed higher levels of fat concentrations in the liver and was insulin resistant. The germ-free group that received microbiota from healthy mice maintained normal glucose levels and sensitivity to insulin. This study showed that different microbiota cause different metabolic responses in animals. It was possible to prevent development of liver inflammation and insulin resistance by implanting microbiota from healthy mice, both indications of liver disease and diabetes, respectively. This type of treatment could have a therapeutic outcome in the future. At present, the intestinal microbiota is considered to be a "microbial organ", with pivotal roles in the body's metabolism and immune functions. Therefore gut transplantation aims to restore gut functionality and re-establish the state of intestinal flora to certain extent.

## Chronic hepatic diseases generate high costs to Europe

Two studies presented at the International Liver Congress 2012 showed the true impact that liver disease has across Europe, one the financial cost of liver disease and the other the high mortality rates associated with cirrhosis.

The former comprised a multicenter, retrospective cost of illness study (COME), to assess costs occurring in 1088 patients over six months. Patients enrolled had liver diseases including hepatitis C, cirrhosis, hepatitis B, hepatic carcinoma and other hepatic diseases (cholestasis, nonalcoholic steatohepatitis, etc.). The study found that liver disease costs in the European Union on average at least €644.77 per patient per month [19]. Hospitalizations account for 50.6 % of the overall mean direct costs per month, with treatment accounting for 41.2 % of costs. In addition, patients and family caregivers lost an average of 1.15 days per patient per month of productivity, an important indirect cost.

The study concluded that although treatment costs account for just over 40 % of direct costs, the use of efficient treatments is required to reduce worsening of patients' health, and the increase of direct and indirect costs. These results demonstrate the real life costs of the treatment and ongoing management of patients with liver disease, a condition increasingly frequent and requiring impact estimates to aid on planning more effective treatment strategies. This might engage health authorities more on investing in preventive actions like reducing harmful alcohol consumption and fighting obesity.

In a separate study, the EASL-CLIF consortium reported that mortality for Acute-on-Chronic liver failure (ACLF) was 35.5 % on day 28 [20]. The consortium set out to address questions around ACLF, a poorly defined syndrome characterized by acute deterioration of cirrhosis, representing a main cause of hospitalization and death. At present, no diagnostic criteria and information on prevalence, pathogenesis or prognosis are available.

Overall, the meeting was useful on discussing emerging approaches for treating hepatitis viruses-related conditions and liver diseases such as diabetes and hepatic fat depot-related diseases, and the impact of current and emerging therapies on a population-wide perspective of the occurrence of hepatic diseases.

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12. Suzuki F, Ikeda K, Toyota J, Karino Y, Ohmura T, Chayama K, *et al*. Dual oral therapy with the NS5A inhibitor Daclatasvir (BMS-790052) and NS3 protease inhibitor Asunaprevir (BMS-650032) in HCV genotype 1B-INFected null responders or ineligible/intolerant to peginterferon/Ribavirin. J Hepatol. 2012;56(Suppl 2):S7-S8.

13. Jacobson I, Lawitz E, Lalezari J, Crespo I, Davis M, Hassanein T, *et al*. PSI-7977 400 MG QD safety and tolerability in the first 450 patients treated for 12 weeks. J Hepatol. 2012; 56(Suppl 2):S441-S41.

14. Gane EJ, Stedman CA, Hyland RH, *et al*. PSI-7977: ELECTRON. Interferon is not required for sustained virologic response in treatment-naive patients with HCV GT2 or GT3. Program and abstracts of the 62nd Annual Meeting of the American Association for the Study of Liver Diseases; November 5-8, 2011; San Francisco, California. Abstract 34.

15. Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis M, DeMicco M, *et al*. ATOMIC: 97 % RVR for PSI-7977+PEG/RBV x 12 week regimen in HCV GT1: an end to response-guided therapy? J Hepatol. 2012;56(Suppl 2):S1.

16. Poordad F, Lawitz E, Kowdley KV, Everson GT, Freilich B, Cohen D, *et al*. 12-week interferon-free regimen of ABT-450/R +ABT-333-+Ribavirin achieved SVR12 in more than 90 % of treatment-naive HCV genotype-1-infected subjects and 47 % of previous non-responders. J Hepatol. 2012;56(Suppl 2):S549-50.

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