Hepatitis B and C
Public Policy Association

NEWSLETTER

DECEMBER 2014 ISSUE

A review of new data on the treatment of chronic hepatitis C presented at The Liver Meeting 2014

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Treatment of chronic hepatitis C was the mainstay at the recent AASLD Liver Meeting in Boston. Although most phase 3 data on the IFN-free combinations of sofosbuvir plus ledipasvir and paritaprevir plus ombitasvir and dasabuvir were presented in April at EASL's International Liver Congress, several compelling real-life data or clinical trials presented in Boston are likely to further advance treatment of HCV in the near future. The data can be divided into three broad categories: Real-life data of approved regimens, fine-tuning of approved regimens and RCTs of experimental drugs. HCV Target provided the most interesting data in the first group of studies as it reported safety and efficacy of sofosbuvir and simemprevir in 2330 patients recruited in the US and Germany. The combination of sofosbuvir plus simeprevir was extremely safe, as only 2% of patients discontinued due to side effects, an especially remarkable feat if one considers that 48% of patients had cirrhosis with an episode of previous decompensation reported in 40% of them. Sofosbuvir plus simeprevir was also highly effective as sustained virological response (SVR) rates were 89% overall with only a minimal impact of cirrhosis, subtype 1a and previous treatment failure to a protease inhibitor on the efficacy rates in subgroup analysis.

In the fine-tuning group of studies, Marc Bourlière from Marseille, France stole the show when reporting a subgroup analysis of phase II-III trials of treatment with sofosbuvir + ledipasvir. This one pill-a-day regimen received FDA approval in the last month, and is expected to receive EMA approval shortly. The FDA label recommends a 24-week treatment course of sofosbuvir plus ledipasvir in treatment-experienced patients with cirrhosis, although this might be optimal in terms of efficacy at the individual patient level, at the population level this strategy might limit access to treatment as drug pricing may be prohibitive for most healthcare systems. By analyzing Phase II-III studies and looking at treatment duration (12 vs 24 weeks) and ribavirin need in 513 cirrhotic patients, Bourlière and colleagues were able to suggest that the addition of ribavirin increased the efficacy of the 12-week schedule of sofosbuvir/ledipasvir to 96% overall, making it as effective as the 24-week ribavirin-free arm (98% SVR). This piece of information has important clinical implications as it highlights that ribavirin still has a place in second-generation interferon-free regimens, as it allows for shorter and cheaper treatment schedules without compromising efficacy.

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Hepatitis B and C Public Policy Association commissioned article is now available

The Hepatitis B and C Public Policy Association's Working Group report on Barriers to care and treatment for patients with chronic viral hepatitis, with George Papatheodoridis and Heiner Wedemeyer as principal investigators, was published as a systematic review article in Liver International earlier this year. **'Barriers to care and treatment for patients with chronic viral hepatitis in Europe: a systematic review'** Liver International ISSN 1478-3223. The report is freely accessible on http://onlinelibrary.wiley.com/doi/10.1111/liv.12565/pdf.

The report was commissioned by the Hepatitis B and C PPA, with non-financial support from EASL and ELPA.

Several new compounds were presented at the Liver Meeting including the second-generation NS5A inhibitor GS-5816 which managed to achieve high SVR rates in combination with sofosbuvir. Still the most compelling data came from the Phase III studies of the combination of grazoprevir (protease inhibitor) plus elbasvir (NS5A inhibitor) and the combination of daclatasvir (NS5A) plus asunaprevir (protesase inhibitor) and beclabuvir (NS5b Non-nucleoside inhibitor). These 2 different interferon strategies managed to reach 90-100% and 93-98% SVR rates, respectively in difficult-to-cure HCV genotype 1 patients with advanced fibrosis or with a previous treatment failure with pegylated interferon-based regimens. Both interferon-free regimens were extremely safe with less than 3% of patients discontinuing due to side effects and without any significant safety signal in these two large Phase III studies. These efficacy and safety rates are not surprising nowadays. Given the fact that in the past limited access to treatment hampered the effectiveness of anti-hepatitis C therapy hence, any new player in the therapeutic field should be viewed positively as this will likely lead to competition between pharma companies, which should translate into a rapid decrease in costs of drugs for healthcare systems. A key factor if broad and equal access to these drugs across Europe is to be achieved.

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The Gilead Sciences Research Scholars Program: An interview with Professor Michael Manns, Chairman of the The Gilead Sciences Research Scholars Committee.

Q1. Could you kindly explain the Gilead Sciences Research Scholars Program for our readership?

The Gilead Sciences Research Scholars Program is a very attractive program for junior researchers to obtain funding to the value of US$ 130,000, which is paid in two annual installments of up to US$ 65,000 each. The Gilead Sciences Research Scholars Program is active in various fields of medicine including cardiovascular disease, primary pulmonary hypertension, cystic fibrosis, haematology and oncology as well as liver diseases. The Liver Disease Research Scholars Program has a North American as well as an International Program. I have the privilege to chair the committee evaluating the applications for the International Gilead Sciences Research Scholars Program. The closing date for applications is 19th January 2015. Detailed information can be obtained at http://researchscholars.gilead.com.

For this program, non-US researchers are eligible to apply. Scholarship awards are awarded annually. The international liver disease program grants up to three awards each year. Applicants who are working and have permanent residency in Europe, Australia, Hong Kong, Japan, Middle East, New Zealand, Singapore, South Korea and Taiwan can apply. The application must contain a description of a research project that should be original and should also be completed within the 2-year funding period. In addition to the description of the research project, the applicant's CV and bibliography should be accompanied by a letter of support from the scientific mentor as well as by the department or division head who has to guarantee a protected time to perform the research project. Proposed research projects should be innovative and should address significant unmet needs in all areas of liver diseases. The applicant should also be able to obtain/secure a faculty position within the next 3 years and should devote his academic career to research in liver diseases.

Q2: As the Chairman of the Committee, what are the features you are looking for when evaluating a research project proposal?

The package of the research proposal consists of the applicant, the mentor, the institution, and the project. We evaluate the applicant concerning his past and present research performance. We also evaluate the originality of the research proposal whether it addresses significant unmet needs in hepatology. We evaluate the mentor as well as the institution where the work is supposed to take part. And finally, we evaluate whether the proposed project can be realistically completed within a 2-year time frame.

Q3: Do you see a shift in research areas now that viral hepatitis will be effectively treated in more than 90% of cases?

If I interpret this question correctly 90% relate to chronic hepatitis C? ! In chronic hepatitis B currently, we can only suppress viral replication. A cure is not yet possible and HBsAg loss in serum is just evolving as the next optimum end-point of treatment - the gold standard, which is as close as we can get to a cure. For chronic hepatitis D we have no specific therapies in place although pegylated interferon has some benefits. We are just learning to understand the role of chronic hepatitis E in the immunosuppressed patient in the Western world.

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Liver cancer, non-alcoholic fatty liver disease (NAFLD) and liver fibrogenesis are further areas where future research efforts have to focussed. And then there is Primary Sclerosing Cholangitis (PSC) the big "black box" in hepatology affecting young people, associated with malignancy, unknown etiology, with no medical therapy..... So as you can see, there is still a lot to do in liver disease research. It will be interesting to see the future applications for the Gilead Sciences Research Scholars' Program for 2015 and beyond.

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How a reduced price for Sofosbuvir was obtained for Egypt

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It is generally acknowledged that Egypt has the highest prevalence of the hepatitis C virus (HCV) worldwide, with a rate of seropositivity as high as 15%. Thus, combating such a disease represents a primary objective on the national agenda. In 2006, in response to this huge burden of HCV infection, a National Treatment Program as part of the National Control Strategy for Viral Hepatitis was launched. This programme aims to provide access to treatment for HCV-infected individuals by offering low-price and even cost-free antiviral medicines. A nationwide treatment network comprising 25 centers was established. They are located all over the country to allow access to patients residing in all Egyptian regions. Training programs were organized to qualify physicians working in these centers, and a standardized protocol was issued by the National Committee for the Control of Viral Hepatitis (NCCVH). This protocol is responsible for overseeing the centers to ensure provision of high standard care and treatment. A specialized network, at the National Committee for Control of Viral Hepatitis was established to interconnect these centers.

The programme started with the standard care treatment for HCV at that time, which was a combination of pegylated interferon and ribavirin therapy. The cost of this treatment regimen was extremely high for a resource-limited country like Egypt. Negotiations with the manufacturing companies of pegylated interferon, and the market competition represented by the presence of a locally produced bio-similar of pegylated interferon have gradually driven down the price reaching 15 percent of its international price. Reducing the cost of therapy has been critical to the success of the Egyptian programme and has improved access to care for individuals with chronic HCV infection that has enabled the programme to treat more than 350,000 patients over the past 7 years.

This maximized Egyptian experience in providing mass treatment for patients with chronic disease, in which the treatment duration lasts up to one year, along with the international publications, as well as the presentations of Egyptian hepatologists at international meetings, have all led to global awareness of the HCV problem in Egypt. Discussing the Egyptian situation with international organizations (WHO, UNICEF, etc.) and stakeholders paved the way to seeking the up to date standard of care for those patients according to the most updated international guidelines. As a result, the Egyptian Government represented by NCCVH, negotiated an agreement for the introduction of Sofosbuvir in Egypt with a 99% discount on the U.S. price. However, the drug will still cost $900 for a 12-week course of treatment; which is a fraction of the $84,000 charged for a course of treatment in the United States. The reduced price will apply to Sofosbuvir supplies used in official treatment centers only, and the access programmes start in late 2014, following completion of registration procedures in Egypt. A standardized protocol, tailored to adapt to the Egyptian situation as well as priority for treatment protocol have been issued. Furthermore, precautions to ensure proper and strict utilization of the drug within the official treatment centers will be applied. We hope that Sofosbuvir will have a major impact on public health in Egypt, by significantly increasing the number of people who can be cured of HCV.

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Chronic hepatitis E virus infection

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Over the last few years, interest in HEV infection, endemic in developing countries, has increased in the developed world [1]. Indeed, the genotype-3 hepatitis E virus (HEV 3) has been shown to be responsible for self-limiting infection in non-compromised patients [1 2]; however, it can lead to chronic hepatitis in all situations of immune deficiency: solid-organ transplant (SOT) patients [3], HIV patients with low CD4-cell counts [4], and hematological patients receiving chemotherapy [5].

Chronic genotype HEV 3 infection has been suspected or clearly shown to be responsible for several extra-hepatic [6, 7, 8] and hepatic manifestations. Neurological symptoms, mainly peripheral nerve involvement, have been observed in immunocompetent and SOT patients infected by HEV 3 [6, 7] and, interestingly, HEV clearance induces complete or partial resolution of neurological symptoms [6]. Very recently, cases of HEV 3-induced glomerulonephritis have been reported in kidney-transplant patients 9 yet cryoglobulinemia disappeared after HEV clearance [9]. We also observed a clear case of HEV 3-associated lymphoma with detection of the virus in the cutaneous tumor, its remission under ribavirin and its clinical recurrence with virologic relapse (work in progress, June 2014).

The main issue with HEV 3 chronic infection remains the risk of chronic active hepatitis with rapidly evolving cirrhosis which may require liver transplantation [10] and re-transplantation in viremic-liver patients may re-induce chronic HEV infection [11].

In a large cohort of SOT patients, HEV infection occurring after transplantation evolved to chronic infection in two-thirds of patients [10]; nearly 10% developed cirrhosis within a short time period [10]. In contrast, no HEV reactivation was observed after kidney re-transplantation in patients who have been cleared of the virus [12]. Hence, in patients chronically infected by HEV, clearance should be achieved to avoid progression of liver fibrosis and occurrence of extra-hepatic manifestations.

To date, there is no established therapy for HEV infection. Reducing immunosuppression, mainly immunosuppressants that target T-cells, has achieved HEV clearance in nearly 30% of SOT patients with chronic hepatitis [10]. Small case series and case reports in this setting have also shown the efficacy of peg-interferon (peg-INF) alone or ribavirin as a monotherapy [13-14] with promising results provided with a short course. We have recently reported data collected from several transplant centers in France including the largest number of solid-organ-transplant patients infected by HEV and treated by ribavirin alone (n = 51) [15]. Our study clearly assessed the efficacy and safety of ribavirin for three (1–18) months as a monotherapy to treat chronic HEV infection. A sustained virological response (SVR) was observed in 82% of patients and the SVR rate did not differ significantly between patients who had received ribavirin therapy for ≤3 months (67% of patients) and those who had received ribavirin for >3 months. The end of treatment virological response was 98%: only one patient was a non-responder who remained viremic when he was retreated after a washout period, suggesting the presence of a ribavirin-associated resistant variant. The only independent predictive factor of SVR was a high lymphocyte count at the initiation of ribavirin therapy (OR 1.002, CI95% 1–1.004, p=0.03) and this is in line with recent evidence that the use of tacrolimus, a more potent immunosuppressant than cyclosporine A, was found to be an independent predictive factor for chronic HEV infection after SOT [11]. In relapsers (12%), most of those who completed a second and prolonged course of ribavirin achieved SVR.

A few reports also suggest that ribavirin has a beneficial effect in patients with severe acute HEV infection and in patients with acute chronic hepatitis.

Finally, an unsolved issue is the cause of the high prevalence of HEV 3 infection in STO, in addition to the food-related route of transmission. HEV 3 infection may be transmitted by transfusion of red blood cells and platelets and the prevalence of anti-HEV antibodies ranges from 10-50% in blood donors and 10% of plasma fractionated pools (1000 donors) test positive for HEV-RNA but are pathogen-inactivated with solvent-detergent incubation or Amotosalen. We recently performed a retrospective study in 347 kidney-transplants (from October 2010 to December 2012), including 48 (14%) treated with TPE. The prevalence of anti-HEV IgG antibodies was 31% (83/267)(works in progress submitted to AASLD 2013). Ten per cent of patients had evidence of post-transplant HEV infections (25 anti-HEV IgG seroconversions and 1 chronic HEV infection without seroconversion): 19 and 8% of patients treated with TPE or not, respectively (P=0.035). Only two patients treated with TPE developed chronic HEV infection and all patients who developed HEV infection without TPE had all received red blood cells. In summary, TPE, like blood transfusion, is a route of transmission of HEV. Since pathogen-inactivated plasma pools, including those using the last generation inactivating products, may transmit HEV, plasma pools should be tested for HEV, especially those destined to SOT recipients and other susceptible recipients.

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