Hepatitis B and C
Public Policy Association
NEWSLETTER

MARCH 2012 ISSUE

Dear Reader,

Let me briefly introduce the first issue of the newsletter of the Hepatitis B and C Public Policy Association. This letter, which has been primarily conceived to inform stakeholders of the Association's activities, will also host contributions from opinion leaders commenting on major scientific and political breakthroughs in the fight against viral hepatitis and its consequences.

Promoting awareness of the consequences and the available instruments to prevent and cure hepatitis will help achieve the United Nations' 2015 Millennium Development Goal of combatting infectious diseases, including hepatitis.

Massimo Colombo, Editor

World Health Assembly Resolution on Chronic Viral Hepatitis (May 2010)

- TO PREVENT the transmission of hepatitis virus through safe and effective health strategies
- TO IDENTIFY AND TREAT those people most at risk for hepatitis virus-related disease with safe and effective therapies
- TO INTEGRATE proven public health strategies for preventing viral hepatitis across the health system
- TO INNOVATE by developing new vaccines and technologies for use in viral hepatitis prevention

A short presentation of Hepatitis B and C Public Policy Association

In April 2009 a group of leading European scientists, professors, public health experts and patient advocates set up the Hepatitis B and C Summit Conferences Association as a not-for-profit Association to urge public policies for the prevention, diagnosis and treatment of hepatitis B and C in the European Union. Its unique approach would be to gather together and work jointly with the main stakeholders in hepatitis B and C – including patients, clinicians, public health experts, regulators, civil society communities and the private sector – and in alignment with the broad programmes already underway at European level.

The Association aimed primarily to deliver a summit conference on hepatitis B and C in Europe which would gather together these major stakeholders, present new and existing data, and promote a European-wide strategy on the prevention and management of these diseases. The Conference was held in Brussels in October 2010 under the auspices of the Belgian EU Presidency. For information about its agenda, speakers, advisors, sponsors, reports launched and presentations made there, please consult the Conference website on http://www.hepbcppa.org/2010-summit-conference.

The October 2010 Conference launched a Call to Action which was endorsed by the major European stakeholders including the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the Viral Hepatitis Prevention Board (VHPB), the World Hepatitis Alliance (WHA), the International Centre for Migration, Health and Development (ICMHD), the European Association for the Study of the Liver (EASL), and the European Liver Patients Association (ELPA). Its text was approved by the European Commission's Directorate-General for Health and Consumers (DG SANCO) and by the European Centre for Disease Prevention and Control (ECDC).

The document, which can be found on http://www.hepbcppa.org/2010-summit-conference, calls for the adoption of the following measures within the European Union:

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Enquiries to: Hepatitis B & C Public Policy Association asbl | email: office@hepbcppa.org
www.hepbcppa.org

1. Improving awareness of the threat posed by hepatitis B and hepatitis C

2. Integrating prevention programmes for hepatitis B and hepatitis C into existing public health frameworks

3. Enhanced surveillanc e for hepatitis B and hepatitis C across Europe

4. Supporting the development and integration of cost-effective technologies and procedures for use in viral hepatitis prevention, control and management, including screening of high risk individuals according to scientific and epidemiological based evidence

5. Ensuring universal access to early counselling and treatment for persons infected with hepatitis B or hepatitis C

6. Expansion of research resources for hepatitis B and hepatitis C.

The Journal of Viral Hepatitis published an independent supplement devoted to the Conference on Hepatitis B and C in Europe in August 2011.

It is freely available on: http://onlinelibrary.wiley.com/doi/10.1111/jvh.2011.18.issue-s1/issuetoc.

In June 2011 the Association changed its name to Hepatitis B and C Public Policy Association to reflect its continuing activities and broader scope. Its aim remains to urge and facilitate the formulation of public policies at national and international level for the communication, prevention and management of the spread of viral Hepatitis B and C. Its approach in furtherance of this aim remains to gather together, and work in partnership with, the major stakeholders in the field of these diseases. The Association will also continue to work in alignment with the WHO and the European Commission in this field, offering its independence and flexibility in support of the development of their often medium- or long-term programmes. Through its emphasis on public policy, the Association will also support the work of EASL and ELPA in Europe.

From 2011, the Association is extending its work to communicate the message contained in the Call to Action issued in 2010 to a broader geographical area. Its planned activities in 2011 and 2012 in the European Union and beyond include (but are not limited by):

1. Conference on Hepatitis B and C in the Mediterranean Basin + Balkan Countries

The Association believes that the objectives listed in the 2010 Call to Action are equally relevant for the broader region of the Mediterranean Basin and the Balkan countries, where the spread of Hepatitis B and C constitutes a very significant burden, and is expanding its initiative to this large area. Specifically the Association will organise a Summit Conference in end-2012 which will gather the major stakeholders in the field of hepatitis B and hepatitis C in the Mediterranean Basin and the Balkan countries to hear new data on the spread and management of these diseases and to launch a Call for Action tailored to the needs of the region, which has been previously approved by the range of stakeholders there.

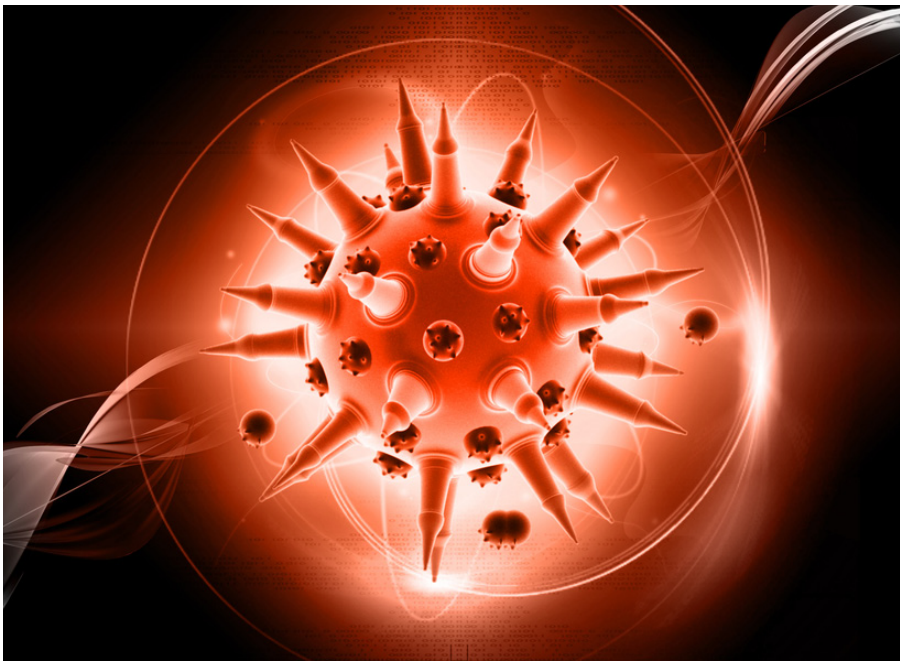
The countries invited to participate at this major event will be: Albania, Algeria, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Egypt, France, FYROM, Greece, Israel, Italy, Jordan, UN-administered territory of Kosovo, Lebanon, Libya, Malta, Montenegro, Morocco, Romania, Serbia, Slovenia, Spain, Syria, Tunisia, Turkey.

This conference will support the European Commission's ongoing work in the field as well as the Resolution on Viral Hepatitis adopted at the 63rd World Health Assembly in May 2010.

2. National level activities

The Association is ready to encourage and participate in national level activities on Hepatitis B and Hepatitis C which will further the message of the Call to Action.

A series of activities will be delivered in Greece in late 2011 and in 2012.



3. Bringing data into the public domain

For example, the Association is producing an extensive slide collection based on the material presented at the October 2010 Conference as a public tool, freely downloadable from the Association's website.

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The Association's output, based on the expertise of its members and of participating non-members, will be maximised through the operation of its Working Groups in 3 areas:

4. Newsletter

The Association's Newsletter will briefly summarize the most recent data on epidemiology, prevention, public policy and therapeutic and diagnostic improvements for Hepatitis B and C. It will be aimed at national and multi-lateral health authorities and regulators, advocacies including patients' associations, and the general media as well as general practitioners and hepatologists. It will be circulated via the Web and on paper, in English with translations into other languages if funds permit.

Massimo Colombo, Co-Chair of the Hepatitis B and C Public Policy Association, will lead the Newsletter's editorial team of leading international experts in viral hepatitis research.

5. Viral Hepatitis as a Millennium Development Goal

This Working Group will hold an invitation-only high-level meeting of international policy experts in the field in London in December 2011 which will discuss the inclusion of viral hepatitis in the Millennium Development Goals. It is led by Charles Gore, Co-Chair of the Hepatitis B and C Public Policy Association and Howard Thomas, founder member of the Association.

6. Migration and Hepatitis

This Working Group will be led by Manuel Carballo, founder member of the Association.

More information on the Association can be found on its website www.hepbcppa.org.

Prepared by Marilyn Clark[1], Angelos Hatzakis[1],[2]
[1] Hepatitis B and C Public Policy Association
[2] Professor of Epidemiology & Preventive Medicine, Director of Dpt of Hygiene, Epidemiology & Medical Statistics, Athens University Medical School, 75 Mikras Asias st, Athens, 11527, Greece, ahatzak@med.uoa.gr | ahatzakis@hepbcppa.org

A quick chat with Prof. Christoph Sarrazin and Dr. Alessio Aghemo analyzing the German and Italian realities on triple therapy with Boceprevir or Telaprevir for patients with chronic hepatitis C.

Q: Prof. Sarrazin could you briefly explain to us how triple therapy is currently regulated in Germany?

Triple-therapies with Boceprevir and Telaprevir in combination with PEG-interferon alfa 2a/b and ribavirin are approved and available for patients with HCV genotype 1 chronic hepatitis C in Germany since July and September 2011, respectively. The costs for 12 weeks Telaprevir are 36 462 EUR and costs for Boceprevir range between 23 921 EUR and 43 855 EUR for 24 to 44 weeks of treatment. Triple-therapies will be fully reimbursed by health insurance companies in Germany for the first year after approval. However, according to a new law (AMNOG) the pharmaceutical industry is requested to provide evidence for a substantial benefit of triple-therapies in comparison to the current treatment options and for long-term end-points (death, liver cancer, quality of life). Based on a rating by the German Health Authorities (GBA) prices for the protease inhibitors then either will stay the same or have to be reduced.

Q: Are the drugs prescribed in accordance to the EU label or does Germany follow specific local guidelines?

The German Guidelines for management of HCV infection will be updated in 2012. However, an expert panel summarized the most important information on the practical use and recommendations for triple therapies in a review which will be published in the German Gastroenterology Journal in December 2011 / January 2012 (Sarrazin et al., Z Gastroenterol in press). Generally, the expert panel recommends application of triple-therapies according to the approval by the EMA. However, a "lead-in" phase to assess the tolerability and sensitivity to PEG-interferon / ribavirin can be performed irrespective of the choice of the protease inhibitor. This may lead to a protease inhibitor spearing regimen in 10-15% of treatment naïve patients. It is important to discuss this strategy in advance with the patient as usually patients have great expectations to be treated with a new direct antiviral agent.

Q: Is IL28B testing used to select patients to receive triple or dual regimens?

Currently, IL28B genotyping is not performed regularly before initiation of antiviral treatment in Germany. The main reason is the lack of consequences for the management of antiviral therapy. Results of future studies may change the importance of IL28B genotype for determination of treatment duration.

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Q: Prof Sarrazin do you think that the new triple therapy regimens will bring upon us any new issues?

Many patients who waited for months or even years to receive DAA-based triple-therapies now will start antiviral treatment with Boceprevir or Telaprevir and overall, a significant increase of the number of treated patients in Germany is recognized. However, due to restricted virologic response rates in null-responders and patients with advanced cirrhosis, significant side effects, drug-drug-interactions associated with the protease inhibitors as well as due to results of phase 2 clinical studies on all-oral and quadruple therapies also a significant number of patients decide to wait for the next generation of DAA-based therapies. Decision on triple therapy with Boceprevir or Telaprevir should be based on the urgency according to the stage of liver disease on the one hand and the individual prediction on virologic response on the other hand.

Finally, one major problem in Germany still is the large number of patients with chronic hepatitis C who do not know about their infection. There is no national screening program and diagnosis of HCV infection mainly depends on HCV antibody testing by general practitioners. It is estimated that only approx. 40% of patients with chronic hepatitis C in Germany are diagnosed.

Q: Dr. Aghemo what about Italy? Are there any differences with the German reality?

Telaprevir (TVR) and Boceprevir (BOC) are expected to become available in Italy in late 2012. This 1 year delay compared to other European countries, is due to the necessity to define the reimbursability rules by the Italian national health system. In the meantime, the launch of an expanded access program for TVR for patients with advanced fibrosis and the possibility to request either BOC or TVR for compassionate use, has effectively allowed a selected group of Italian patients to receive the new drugs.

Q: Has this 1 year delay had any impact on the management of Hepatitis C patients?

Unfortunately, this 1 year delay has magnified what was already present in the last years, the so called warehousing effect. Basically, many HCV-1 patients have been left untreated and put on a waiting list, the "warehouse", to receive treatment only once TVR/BOC become available. Although this might seem logical for patients with a mild disease without any extra-hepatic manifestations of HCV, this strategy is likely to backfire once the drugs enter the Italian market. First of all it seems highly probable that the Italian legislator in the attempt to contain health care costs will impose some limits on the reimbursability of the two drugs, effectively limiting TVR/BOC only for patients with advanced fibrosis/cirrhosis or for those who have already failed a previous course of Peginterferon plus Ribavirin. The "warehoused" patients obviously need to be informed about this possibility as it is likely that most of them will not meet these criteria. Secondly, keeping patients in the warehouse further amplifies unrealistic patients expectations for the efficacy and tolerability of TVR/BOC based regimens. Most patients are indeed under the impression that they will receive an all oral Interferon free regimen that not only will dramatically increase the efficacy rates but also somewhat be relatively adverse event free.

Q: This seems to be a common problem as Christoph Sarrazin pointed out it is also present in Germany, do you have any idea why?

It is probable that this misinformation derives not only from the media reporting incomplete data, more often than not due to commercial bias, but also because to date, only a small number of centers in Italy have actually treated patients with TVR/BOC, with the consequence that many hepatologists aren't completely aware of the small nuances that the correct management of these drugs will require. Indeed, it is rather frequent to witness that, once patients are told properly about the benefits and limits of the new drugs, they will often concur that waiting is not the best therapeutic approach.

Q: What should be done to take advantage of this 12 month delay in the arrival of triple therapy regimens?

Personally, I think that until TVR/BOC become available in Italy, scientific societies and patients organizations should work in parallel to inform and to train hepatologists on the correct clinical management of these drugs as well as the fundamental role of the patients selection process, while concurrently informing patients of the potential limitations and side effects of the first generation of HCV protease inhibitors, with the ultimate aim to improve effectiveness of anti-HCV therapy in late 2012. To reach this goal, some Italian regions are setting up regional networks clustered around tertiary clinical centers that can provide the technological and clinical know-how, necessary to manage TVR/BOC, to smaller centers. Although this is an ambitious goal, it should finally allow for equal access to speciality care in Italy whilst also allowing patients to be correctly managed locally.

Should we use Entecavir or Tenofovir in patients with chronic hepatitis B undergoing immunosuppressive chemotherapy? A quick expert opinion by Prof. Harry L.A. Janssen and Dr. Milan Sonneveld

Q: Could you briefly summarize the current standard of care therapy for patients with chronic Hepatitis B?

The treatment of chronic hepatitis B (CHB) has been revolutionized with the introduction of entecavir (ETV) and tenofovir (TDF). Both agents have shown to be superior to older nucleo(s)tide analogues for the treatment of CHB, with most patients achieving undetectable HBV DNA levels during treatment and virtually no antiviral resistance through up to 5 years of continuous therapy. The superiority of the newest agents was confirmed in a recent meta-analysis. A drawback of both ETV and TDF is that both agents are considerably more costly than older agents such as LAM, raising the question whether ETV or TDF are the optimal choice of first-line treatment in all CHB patients.

Q: What is the specific issue with immunocompromised patients?

Well reactivation of CHB in immunocompromised patients, defined as reappearance of active necro-inflammation in the liver after documented inactive HBsAg carriage or serologically resolved hepatitis B, is an often severe condition that may progress to liver failure and death. The risk of reactivation is particularly high in patients receiving immunosuppressive chemotherapy comprising biologicals such as rituximab. Reactivation in patients treated with immunosuppressive drugs typically manifests with a rise in HBV DNA, followed by a flare of ALT. Importantly, reactivation may occur both in patients with positive HBsAg, as well as those with negative HBsAg (even in the presence of anti-HBs) but with positive anti-HBc. A large systematic review has shown that preventive treatment with LAM in HBsAg-positive patients undergoing chemotherapy may reduce the risk of HBV reactivation and associated morbidity and mortality, and prophylactic treatment is superior to ALT or HBV DNA guided treatment in HBsAg positive patients.

Q: It seems therefore logic that LAM should be the drug of choice, or are we missing something?

Actually not all reactivations can be prevented with LAM, and prolonged LAM based therapy will result in antiviral resistance in a significant proportion of patients. The question therefore remains whether results can be improved by using ETV or TDF. In a comparative study, patients treated with ETV had a somewhat lower probability of reactivation than patients treated with LAM and another case series showed that ETV therapy may successfully prohibit HBV reactivation. Based on the available data, current European Association for the Study of the Liver treatment guidelines recommend use of ETV and TDF for prevention of reactivation in HBsAg-positive patients, except in those with very low or undetectable viral load, where LAM might be considered. Since both ETV and TDF are considerably more costly than LAM, a rise in costs for the management of HBV in immunocompromised patients is to be expected. Recent cost-effectiveness studies in CHB patients have shown that use of the most potent agents with the lowest risk of antiviral resistance is effective in reducing HBV related mortality, and is in fact both cost-effective and even cost-saving when compared to use of agents with a lower barrier to resistance. These findings are supported by another cost-effectiveness study from an Italian perspective. Given that these findings hold true even in an HBeAg-negative population with a relatively low viral load (where risk of resistance is generally reduced), it stands to reason that application of agents with a high barrier to resistance in HBV infected patients with a detectable viral load undergoing immunosuppressive treatment is also the most appropriate. In our opinion, prophylactic therapy with ETV or TDF should therefore be initiated in all HBsAg-positive patients undergoing immunosuppressive chemotherapy, especially in patients that will require prolonged treatment. LAM may be an option in patients with very low or undetectable HBV DNA where risk of resistance is negligible and short duration of treatment is anticipated.