Hepatitis B and C
Public Policy Association
NEWSLETTER

NOVEMBER 2012 ISSUE

Dear Colleagues,

The 3rd issue of the 2012 newsletter conveys the message by Prof. Mark Thursz, EASL Secretary General, commenting on the successful outcome on the very recent EASL/AASLD Special Conference on Therapy of Hepatitis C: Clinical application and drug development held in Prague. We then switch to HDV infection, with the discoverer of the virus Prof. Mario Rizzetto from Turin, explaining us the past, present and future of HDV infection. Prof. Fabien Zoulim from Lyon will then answer some questions in a quick Q & A session focused on the impact of HBV vaccination. Finally Prof. Angelos Hatzakis will introduce the Conference on Hepatitis B and C in Mediterranean and Balkan Countries which will take place in Cyprus on the 5th-7th December 2012 and that we hope most of you will be able to attend.

*Alessio Aghemo*
*Massimo Colombo*

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

## EASL's Activities

*Prof. Mark Thursz, EASL Secretary-General*

### HCV: new drugs and new paradigms

As Secretary-General of EASL I get to attend a large number of conferences but none has left me feeling as optimistic as the recent EASL/AASLD Special Conference on Therapy of Hepatitis C: Clinical application and drug development. Only eighteen months ago Anna Lok presented a proof-of-concept study at the International Liver Congress demonstrating that HCV could be cured without the need for interferons. Since then a number of studies have confirmed this finding and have gone on to show, particularly in naive patients, that high rates of sustained virological responses can be achieved with direct acting antivirals. In parallel with these interferon-free studies there are also numerous triple and quadruple therapy regimens combining direct acting antivirals with pegylated interferon and ribavirin which demonstrate high levels of SVR in both treatment naive and treatment experienced patients. I am looking forward to the time when the heartsink consultation with a patient who failed antiviral therapy is a rarity.

The Special Conference was the first opportunity that the clinical community has had to review all the data on direct acting antivirals that has emerged over the last 5 years. It is clear at this stage that nothing is clear about the future treatment of HCV. Two important direct antivirals have been subjected to a clinical development hold by regulatory authorities in the last 6 months and on reflection the number of patients in some of the interferon-free trials have been remarkably small. This should arm us with a sense of caution to counterbalance our optimism.

Nevertheless the prospect of interferon-free regimes of relatively short duration and minimal side effects potentially opens up two important areas for therapeutic deployment. Firstly these new regimens may be suitable for

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patients with decompensated cirrhosis leading either to disease reversal or transplantation without viraemia. Secondly a less demanding drug regimen is more suitable for drug users raising the possibility of using treatment to minimise transmission as well as curing the patients.

It is important to recall that no matter how effective the drugs the impact on the burden of disease cannot be realised without screening programmes for case identification.

For this reason we must arm ourselves with the proof that viral hepatitis screening in Europe is cost effective in order to convince the European Commission and Council that screening must be implemented.

**Prof. Mario Rizzetto, Professor of gastroenterology at the University of Turin and Director of the Division of Gastroenterology and Hepatology at the San Giovanni Battista Hospital in Turin, discusses the past, the present and the future of HDV infection.**

***Prof. Rizzetto it has been 35 years since your discovery of the Hepatitis Delta Virus, could you talk to us a bit about that exciting period of time and guide us through the most important advance in the HDV field?***

**The 1970s were a time of excitement in Hepatology. The discovery of the HBsAg in the mid 1960s had provided the key to the secrets of viral hepatitis and in rapid succession the HBV virion was discovered by David Dane (hence the eponim of Dane particle), the core antigen by June Almeida and the e antigen by Lars Magnius. During the early 1970s I had a stage as a young post-doctoral fellow to work on liver autoimmunity at the Middlesex Hospital in London, the same where Dane and Almeida were working.**

On my return to Italy at the end of 1973 the dilemma was whether to continue research in liver autoimmunity, which was of limited impact in our patients, or turn attention to the emerging field of viral diseases, which promised to be the protagonist; fortunately I had learnt in London immunochemical technologies to determine not only autoantibodies but also to detect viral antigens of the HBV in the liver. Starting from 1974 we used in Torino direct immunofluorescence as a tool to determine the HBsAg in the cytoplasm and the HBcAg in the nuclei. We were using home made fluorescent antisera; upon exhaustion of the antiserum source, we were repreparing a new lot. A new lot of putative fluorescent anti-HBc antiserum prepared at the beginning of 1975 gave a nuclear fluorescence somewhat different from the classical HBcAg fluorescence, in that the pattern of granularity was more coarse. At the time, part of the HBcAg- positive liver biopsies were routinely sent for electron microscopy and ultrastructural core particles were regularly detected. Suspecion increased when the Electron Microscopist, Dr. Canese could no longer observe core structures in the samples sent to her as HBcAg positive based on positive nuclear fluorescence with the new antiserum.

We clearly became curious and interested to determine the reason for the discrepancy. Comparison of our strange antiserum with a reference anti-HBc antiserum obtained from Dr. K. Krawczynsky, the polish scientist who first described the nuclear localization of HBcAg immunofluorescence, showed that most liver biopsies either contained HBsAg or the new odd fluorescence. Ultimate proof of a different reactivity came from double staining experiments with the reference anti-HBc antiserum conjugated with fluorescein and with the odd antiserum conjugated with rhodamine, that showed unequivocally that HBcAg and the odd reactivity were localized in different nuclei. The conclusion was a paper in Gut in 1977 where we described a new antigen, called delta, associated with HBV infection and with liver disease, and distinct from known antigens of the HBV.

The true nature of the delta antigen emerged from studies in chimpanzees, the only animal model susceptible to HBV infection and thus to HDV.

From the different expression of delta in the liver of chimpanzees naïve to HBV and in chimpanzees carrying the HBsAg, both inoculated with the same HBsAg

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positive serum containing delta, it became clear that the delta antigen was not a reactivity of the HBV but the hallmark of a new defective RNA virus requiring HBV for establishing its own infection.

This new virus received the name of hepatitis D Virus (HDV).

Subsequent virological studies has shown that HDV is unique in human virology: it is classified in a genus of its own, Deltaviridae. In the appropriate setting, i.e. the carrier of the HBsAg, it may remain infectious at 10-11 serum dilutions, which is the highest infectious titer ever reported for a transmissible agent. HDV is the smallest infectious agent in man (1.700 Kb), contains within its RNA genome a segment of less than 100 bases that can as a catalyst self-cleave and self-bind the RNA molecule, thus behaves as a ribozymes, it replicates in a way unknown to human viruses through a double rolling circle mechanism producing multimeric linear intermediates that are cut to monomeric units and circularised to infectious RNA by the ribozyme.

Most important, HDV hijacks to its advantage the replicative machinery of the hepatocyte. Conventional RNA viruses undergo replication by a virus encoded RNA-dependent RNA-polymerase; they cannot use human RNA-polymerases, as these accept only DNA templates. However, HDV does not possess an own polymerase; it is replicated by host RNA polymerases, which are redirected to read and copy its RNA as if it were an endogenous DNA.

## Are we right in saying that the incidence of HDV infection in Europe is on the rise?

The perception that HDV is returning implies that its infection had disappeared or had diminished. This is true for Southern Europe and areas of the developed world where HDV was endemic in the 1980s, such as Taiwan. In the past 20 years, universal HBV vaccination, behavioural changes prompted by the fear of AIDS (the human immunodeficiency virus is transmitted in the same ways as HDV HBV), and improved sanitation and living conditions have diminished HBV infection in virtually all countries of the developed world. In Italy, the diminished natality and the reduction of household sizes have also helped to curtail HBV infection. By distancing the network of HBsAg carriers on whom HDV spreads, control of HBV has resulted in the secondary containment of this virus and in consistent changes in the epidemiology of hepatitis D.

However HDV infection has not diminished in most areas of the developing world where HBV remains uncontrolled. The apparent absence of HDV in the past decades in many third-world areas was simply due to lack of testing and the current apparent return is due to the increased attention and to more resources devoted to diagnose this infection.

In the last years, outbreaks of hepatitis D were reported from Russia, Greenland and Mongolia and high rate of HDV have been found in Pakistan, Gabon, Cameroon, Nigeria, Tajikistan, Mauretania, Iran, indicating that hepatitis D remains a scourge and a major medical problem in developing countries.

A major public health campaign is needed to raise attention to the neglected medical problem of hepatitis D in the poorest countries of the world and to provide assistance and prevention strategies under difficult local conditions.

## What is the relevance of hepatitis D in Europe in terms of epidemiology and treatment options?

In terms of disease severity it is important to understand that most of the patients collected in the 70s and 80s had a florid liver disease connoted by a picture of chronic active hepatitis at histology. Inactive cirrhosis residual to burnt-out inflammation was seen in less than 20% of HDV cases collected at referral medical units in Italy.

The epidemiological changes had a major impact on the clinical features of HDV disease in Southern Europe. Due to the diminished circulation of HDV, the occurrence of new and fresh forms of hepatitis D has greatly diminished and the medical scenario is now dominated by advanced fibrotic HDV disorders.

However, the impact of HDV on morbidity and survival remains high in developing countries, where the clinical features of HDV infected patients are the same as the florid features seen in Southern Europe in the 1980s.

The medical problem is formidable in terms of therapy; there is no enzymatic protein to be targeted by antiviral therapy, as is the case for hepatitis B and C. Peg-IFN is the only approved therapy but unfortunately it controls hepatitis D only in about 20% of cases and is aggravated by a high rate of virological relapse.





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## Q & A session about the worldwide and European impact of HBV vaccination with Prof. Fabien Zoulim, Head of Hepatology Department at the Hospices Civils de Lyon, France, Head of Viral Hepatitis Research Team, INSERM U1052, and Professor of Medicine, Lyon University.

***Q: Prof. Zoulim, could you quickly sum up the history of the anti-HBV vaccination program and tell us what you think were the main milestones?***

Efforts to develop a vaccine have started right after the discovery of hepatitis B surface antigen and the virus in the seventies. Initially, the vaccine was derived from the plasma of inactive carriers and subsequently the progress of molecular biology allowed to develop a recombinant vaccine in the early eighties. Because of the epidemiology of HBV infection and the public health burden of the disease, a mass vaccination program was started in all neonates in Taiwan in the mid-eighties. 10 years after the implementation of this program, the prevalence of HBsAg in children had decreased dramatically to approximately 10% to 0.8%. In parallel, the incidence of hepatocellular carcinoma in the young population had decreased. This was the first proof that a mass vaccination program was effective to decrease the prevalence of chronic HBV infection at the level of a population and that it could also prevent the occurrence of liver cancer. Other mass vaccination programs were started later on with success in Alaska and in Italy for instance. In other countries vaccination was implemented in young adolescent as a catch-up program and in young children in the primary vaccination program.

***Q: Is the anti-HBV program working in Europe, or are there some categories of patients that still escape vaccination?***

In Europe, the example of Italy has been successful as it was associated with a decline in HBV infection prevalence over the last twenty years allowing to move the country from a middle prevalence area to a low prevalence area. In France, the situation was more complex as mass vaccination program was started in young adolescents entering secondary school and large proportion of the population was vaccinated in a short period of time. However, because of the occurrence of cases of multiple sclerosis like syndromes, enthusiasm dropped significantly in the general population as well as in general practitioners despite the absence of scientific evidence of a causal link. All efforts should be made to continue the mass vaccination programs as this is one of the unique example of an efficient vaccine that can not only prevent the establishment of chronic infection but also cancer.

***Q: Do you think it is reasonable to hope for HBV eradication in some low prevalence areas of Europe?***

There are several difficulties in the path towards eradication of HBV which include the need: 1) for a complete population coverage, 2) to target resource poor populations which are at increased risk of HBV infection, 3) to improve access to healthcare and vaccine of poor populations and immigrants.

# Summit Conference
# Hepatitis B and C in Mediterranean and Balkan Countries

5-7 December 2012 Nicosia Cyprus

The **high-level stakeholders' Conference on Hepatitis B and C in Mediterranean and Balkan Countries** which will take place in Cyprus on 5th-7th December, 2012 under the auspices of the Cyprus EU Presidency (www.hepsummit2012.org) will address the urgent need to prevent, diagnose and treat hepatitis B and C in this large region where the burden of these diseases is significant. It will present both new and existing data and permit targeted discussion with the specific objective of promoting common strategies on their prevention and management.

The Conference will highlight and support the Resolution on Viral Hepatitis adopted at World Health Organisation's Assembly of May 2010, as well as the programmes of the European Centre for Disease Prevention and Control (ECDC) and the US Centres for Disease Control and Prevention (CDC). The Conference will launch a Call to Action tailored to the needs of this region where the text will have been agreed in advance by the major international stakeholders.

**LIVE STREAMING** of the Conference proceedings will be freely available between 5th and 7th December, 2012 at the times given on the Conference programme.

The Advisory Board to the Conference consists of:

- Dr. Marita van de Laar – European Centre for Disease Prevention and Control/ECDC.
- Dr. Kevin Fenton – US Centre for Disease Control and Prevention/CDC.
- Dr. Pierre van Damme – Viral Hepatitis Prevention Board.
- Dr. Martin Donoghoe – World Health Organisation, Europe.
- Dr. Lucas Wiessing – European Centre for Monitoring of Drugs and Drug Addiction.

Members of its Steering Group are:

- Prof. Angelos Hatzakis – Athens University, Co-Chair.
- Charles Gore – World Hepatitis Alliance, Co-Chair.
- Prof. Michael Manns – Hannover University, Co-Chair.
- Dr. Nabil Antaki – Saint Louis Hospital, Aleppo, Syria.
- Prof. Maria Buti – Hospital Val d'Hebron, Barcelona, Spain.
- Dr. Manuel Carballo – International Centre for Migration, Health and Development.
- Prof. Massimo Colombo – Milan University, Italy.
- Prof. Antonio Craxi – Palermo University, Italy.
- Prof. Gamal Esmat – Cairo University, Egypt.
- Achim Kautz – European Liver Patients Association/ELPA.
- Prof. Daniel Shouval – Hadassah University Hospital, Jerusalem, Israel.
- Prof. Nurdan Tozun – Acibadem University, Turkey.
- Prof. Mark Thursz – European Association for the Study of the Liver/EASL.
- Dr. Lia Vounou – for Cyprus EU Presidency.

The Conference organizer, the Hepatitis B and C Public Policy Association asbl (www.hepbcppa.org), is a Luxembourg-based not-for-profit association set up in 2009 to urge and facilitate the formulation of public policies at national and international level for the communication, prevention and management of viral hepatitis B and C. The Association's unique approach is to gather together and work in partnership with all the major stakeholders in the field of these diseases.

Target countries for the Conference on Hepatitis B and C in Mediterranean and Balkan Countries are: Albania, Algeria, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Egypt, France, FYROM, Greece, Israel, Italy, Jordan, Lebanon, Libya, Malta, Montenegro, Morocco, Portugal, Romania, Serbia, Slovenia, Spain, Syria, Tunisia, and Turkey.

Keynote addresses at the Conference will be provided by:

- World Health Organisation – European Region.
- World Health Organisation – Eastern Mediterranean Region.
- European Centre of Disease Prevention and Control (ECDC).
- US Centers for Disease Control and Prevention (CDC).

The Conference agenda is available on its website www.hepsummit2012.org.

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